Protocol I1F-MC-RHCH

A Multicenter, Randomized, Double-Blind and Placebo-Controlled 16-Week Study Followed by Long Term Evaluation of Efficacy and Safety of Ixekizumab (LY2439821) in Chinese Patients With Radiographic Axial Spondyloarthritis

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Ixekizumab (LY2439821)

Study I1F-MC-RHCH is a Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group, outpatient study to evaluate the efficacy and safety of ixekizumab (LY2439821) versus placebo at 16 weeks in Chinese patients with radiographic axial spondyloarthritis (r-axSpA). Patients will be randomized to subcutaneous (SC) placebo, or ixekizumab. This study will also evaluate long-term efficacy and safety of ixekizumab during an Extended Treatment Period (36 weeks). All patients entering into the Extended Treatment Period from the placebo treatment group will receive ixekizumab 80 mg Q4W.

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Protocol Electronically Signed and Approved by Lilly on date provided below.

Approval Date: 20-Jun-2019 GMT

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1. Synopsis

Title of Study:

A multicenter, randomized, double-blind and placebo-controlled 16-Week study followed by long term evaluation of efficacy and safety of ixekizumab (LY2439821) in Chinese patients with radiographic axial spondyloarthritis

Rationale:

Ixekizumab (LY2439821) is a humanized immunoglobulin G subclass 4 (IgG4) monoclonal antibody (MAb) that neutralizes the cytokine interleukin-17A (IL-17A, also known as IL-17). Strong scientific evidence exists indicating an important role of the IL-23/IL-17 pathway in axial spondyloarthritis (axSpA) pathogenesis (Baeten et al. 2010, 2014a; Maksymowych 2010; Baraliakos et al. 2011; Reveille 2011; Yeremenko et al. 2014). Pivotal studies of ixekizumab have recently demonstrated the efficacy of blocking IL-17A in the treatment of radiographic axial spondyloarthritis (r-axSpA; ankylosing spondylitis [AS]) in biological disease-modifying antirheumatic drug (bDMARD)-naïve as well as in tumor necrosis factor (TNF) inhibitor experienced patients (van der Heijde et al. 2018; Deodhar et al. 2019b).

Objective(s)/Endpoints:

Objectives	Endpoints
Primary • The primary objective is to compare ixekizumab 80 mg every 4 weeks (Q4W) versus placebo in bDMARD-naïve patients with active radiographic axial spondyloarthritis (r-axSpA) at Week 16	• Proportion of patients achieving an Assessment of Spondyloarthritis International Society 40 (ASAS40) response
Major Secondary • To compare ixekizumab 80 mg Q4W to placebo in overall study population at Week 16	• Proportion of patients achieving an ASAS40 response • Proportion of patients achieving an ASAS20 response • Change from baseline in Ankylosing Spondylitis Disease Activity Score (ASDAS) • Change from baseline in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) • Change from baseline in Bath Ankylosing Spondylitis Functional Index (BASFI) • Proportion of patients achieving ASDAS < 2.1 • Change from baseline in magnetic resonance imaging (MRI) of the spine (Spondyloarthritis Research Consortium of Canada [SPARCC] score) • Change from baseline in Short Form 36 (SF-36) physical component score (PCS)

Summary of Study Design:

Study I1F-MC-RHCH (RHCH) is a Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group, outpatient study to evaluate the efficacy and safety of ixekizumab 80 mg Q4W subcutaneous (SC) versus placebo in patients with r-axSpA, during a 16-week Blinded Treatment Dosing Period.

Study RHCH will also evaluate long-term efficacy and safety of ixekizumab during the Extended Treatment Period for a total treatment duration of 1 year (52 weeks).

Treatment Arms and Duration:

Study RHCH has 2 treatment groups during the 16-week Blinded Treatment Dosing Period: ixekizumab 80 mg Q4W and placebo at 1:1 ratio. All patients randomized to an ixekizumab treatment group will receive a starting dose of ixekizumab 160 mg at Week 0 followed by ixekizumab 80 mg Q4W thereafter. All administrations are SC. Randomization will be stratified by baseline C reactive protein (CRP) status and prior TNF inhibitor history (if applicable) (i.e., naïve patient with normal CRP, naïve patient with elevated CRP, and TNF inhibitor experienced patient with elevated CRP, elevated defined as >5.00 mg/L)

At Week 16, placebo patients will start receiving ixekizumab 80 mg Q4W with a 160 mg starting dose. All patients will be on an ixekizumab regimen for the Extended Treatment Period (Weeks 16 to 52). The study duration will be up to 1 year for ixekizumab administration, and up to 1 year and approximately 4 months for study participation over 4 periods ([1] Screening Period: up to 42 days; [2] Blinded Treatment Dosing Period: 16 weeks; [3] Extended Treatment Period: 36 weeks; [4] Post-Treatment Follow-Up Period: up to 12 weeks after the date of the patient's early termination visit [ETV] or last regularly scheduled visit).

Number of Subjects:

This study will include approximately 140 randomized patients. Patients are eligible to be included in the study if they have an established diagnosis of r-axSpA with sacroiliitis defined radiographically according to the modified New York (mNY) criteria, based on central reading, associated with ≥1 spondyloarthritis (SpA) feature, and have active disease defined as BASDAI ≥4 and back pain ≥4 on a numeric rating scale (NRS). Patients must have had an inadequate response or a history of discontinuation due to intolerance, as determined by the investigator, to 2 or more nonsteroidal anti-inflammatory drugs (NSAIDs) at the therapeutic dose range (for a total duration of at least 4 weeks) and a history of prior r-axSpA therapy for at least12 weeks. Both bDMARD-naïve and TNF inhibitor-experienced patients can be enrolled.

Statistical Analysis:

Approximately 140 patients will be randomized at a 1:1 ratio in the Blinded Treatment Dosing Period to ixekizumab 80 mg Q4W and placebo. ≥ 61 bDMARD-naïve patients per treatment group will ensure ≥ 90% power to test the superiority of ixekizumab Q4W to placebo for the ASAS40 at Week 16 in bDMARD-naïve patients. The following assumptions were used for the power calculations for ASAS40 response rates in bDMARD-naïve patients at Week 16: 44% for ixekizumab Q4W treatment group and 16% for placebo group. A 2 sided Fisher's exact test at the 0.05 level is assumed. The efficacy analyses for the Blinded Treatment Dosing Period will be conducted on the intent-to-treat (ITT) population, and safety analyses will be conducted on the safety population.

Comparisons between ixekizumab treatment group and placebo will be performed for all analyses in the Blinded Treatment Dosing Period. The primary analysis method for treatment group comparisons of categorical efficacy and health outcomes variables will be a logistic regression analysis with treatment, baseline CRP status (non-elevated or

elevated), and prior TNF inhibitor experienced or naïve as factors (if applicable), using the nonresponder imputation (NRI) method. Under NRI, all nonresponders at Week 16 (Visit 8), as well as all patients who discontinue study treatment at any time prior to Week 16 for any reason, will be defined as nonresponders for the NRI analysis at Week 16. Randomized patients without any postbaseline observation will also be defined as nonresponders for the NRI analysis. A graphical multiple testing strategy for the primary and major secondary objectives will be implemented to control the family-wise type I error rate at a 2-sided α level of 0.05.

The primary analyses for the continuous efficacy and health outcomes variables will be made using mixed-effects model of repeated measures (MMRM) analysis with treatment, baseline CRP status, prior TNF inhibitor experienced or naïve (if applicable), baseline value, visit, baseline value-by-visit, and treatment-by-visit as fixed factors.

A secondary analysis for continuous efficacy and health outcomes variables may be made using analysis of covariance (ANCOVA) with treatment, baseline CRP status, baseline value and prior TNF inhibitor experienced or naïve (if applicable).

Fisher's exact test will be used for all adverse events (AEs), baseline, discontinuation, and other categorical safety data. Continuous vital sign and laboratory values will be analyzed by ANCOVA with treatment and baseline values in the model.

Efficacy, health outcomes, and safety variables during the Extended Treatment Period will also be summarized.

2. Schedule of Activities

	Screening (Period 1)	Baseline Randomization	Blinded Treatment Dosing Period (Period 2)[a]					
CRF Visit (V) Number	V1	V2	V3	V4	V5	V6	V7	V8
Weeks Since Randomization		W0	W1	W2	W4	W8	W12	W16
Study Days	Up to -42 d	0	7 ± 2d	14 ± 2d	28 ± 2d	56 ± 4d	84 ± 4d	112 ± 4d
Informed consent	X							
Demographics[b]	X							
Physical examination[c]	X							X
Vital signs (BP and pulse)[d]	X	X[d]	X	X	X	X	X	X[d]
Weight[aa]	X	X			X	X	X	X
Height		X						
Habits[e]		X						
Body temperature		X						
AP Chest X-ray[f]	X							
Inclusion/Exclusion criteria[g]	X	X						
Evaluate presence of SpA features	X	X						
Randomization		X						
Concomitant medications	X	X	X	X	X	X	X	X
NSAID use	X	X	X	X	X	X	X	X
Preexisting conditions and medical history[h]	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X
Eye symptom assessment[i]	X	X	X	X	X	X	X	X
Dispense IP		X			X	X	X	X
Administer IP on site[j]		X						X
IP compliance[k]					X	X	X	X
Dispense SDAL		X			X	X	X	X

	Screening (Period 1)	Baseline Randomization	Blinded Treatment Dosing Period (Period 2)[a]					
CRF Visit (V) Number	V1	V2	V3	V4	V5	V6	V7	V8
Weeks Since Randomization		W0	W1	W2	W4	W8	W12	W16
Study Days	Up to -42 d	0	7 ± 2d	14 ± 2d	28 ± 2d	56 ± 4d	84 ± 4d	112 ± 4d
Collect, review, and enter data from SDAL		X			X	X	X	X
Clinical Efficacy/Health Outcomes								
MRI of spine and SIJ[x]	X[y]							X[z]
X-ray of the spine[cc]	X							
X-ray of the SIJ[j]	X							
Linear BASMI		X				X		X
Chest expansion		X				X		X
Occiput to wall distance		X				X		X
Enthesitis MASES		X				X		X
Patient Global Assessment of Disease Activity NRS	X	X	X	X	X	X	X	X
Spinal pain	X	X	X	X	X	X	X	X
BASFI	X	X	X	X	X	X	X	X
BASDAI	X	X	X	X	X	X	X	X
C-SSRS[m]	X	X	X	X	X	X	X	X
Self-Harm Supplement Form[m]	X	X	X	X	X	X	X	X
FACIT Fatigue Scale	X	X				X		X
SF-36	X	X			X	X		X
ASAS HI	X	X			X	X		X
QIDS-SR16	X	X						X
EQ-5D-5L		X						X
WPAI-SpA		X						X
Laboratory Tests								
HLA-B27[n]	X							
CRP	X[o]	X	X	X	X	X	X	X
Administer PPD/Collect QuantiFERON®-TB Gold/ T-SPOT®[p]	X							

	Screening (Period 1)	Baseline Randomization	Blinded Treatment Dosing Period (Period 2)[a]					
CRF Visit (V) Number	V1	V2	V3	V4	V5	V6	V7	V8
Weeks Since Randomization		W0	W1	W2	W4	W8	W12	W16
Study Days	Up to -42 d	0	7 ± 2d	14 ± 2d	28 ± 2d	56 ± 4d	84 ± 4d	112 ± 4d
ECG	X							
FSH[q]	X							
HIV/HCV	X							
HBV[r]	X[r]	X[r]					X[r]	
Serum pregnancy test[s]	X							
Urine pregnancy test[s]		X	X	X	X	X	X	X
Serum chemistry	X	X			X	X	X	X
PTT, PT/INR	X							X
Lipid panel (fasting)[t]		X						X
Hematology	X	X			X	X	X	X
Urinalysis	X							X
TSH and free T4	X							
Immunogenicity testing[u]		X	X	X	X	X	X	X
PK sampling[u,v]		X	X	X	X	X	X	X

	Extended Treatment Period (Period 3)[a]									ETV
CRF Visit (V) Number	V9	V10	V11	V12	V13	V14	V15	V16	V17	ETV
Weeks Since Randomization	W20	W24	W28	W32	W36	W40	W44	W48	W52	
Study Days	140 ± 4d	168 ± 4d	196 ± 4d	224 ± 4d	252± 4d	280 ±4d	308 ±4d	336±4d	364 ± 4d	
Physical examination[c]									X	X
Vital signs (BP and pulse)[d]	X	X	X	X	X	X	X	X	X	X
Weight[aa]	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X
NSAID use	X	X	X	X	X	X	X	X	X	X
Preexisting conditions and medical history[h]	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X
Eye symptom assessment[i]	X	X	X	X	X	X	X	X	X	X
Dispense IP	X	X	X	X	X	X	X	X		
IP compliance[k]	X	X	X	X	X	X	X	X	X	X
Dispense SDAL	X	X	X	X	X	X	X	X		
Collect, review, and enter data from SDAL	X	X	X	X	X	X	X	X	X	X
Clinical Efficacy/Health Outcomes										
MRI of spine and SIJ[x]									X[bb]	X[z]
Linear BASMI		X			X				X	X
Chest expansion		X			X				X	X
Occiput to wall distance		X			X				X	X
Enthesitis MASES		X			X				X	X
Patient Global Assessment of Disease Activity NRS	X	X	X	X	X	X	X	X	X	X
Spinal Pain	X	X	X	X	X	X	X	X	X	X
BASFI	X	X	X	X	X	X	X	X	X	X
BASDAI	X	X	X	X	X	X	X	X	X	X

	Extended Treatment Period (Period 3)[a]									ETV
CRF Visit (V) Number	V9	V10	V11	V12	V13	V14	V15	V16	V17	ETV
Weeks Since Randomization	W20	W24	W28	W32	W36	W40	W44	W48	W52	
Study Days	140 ± 4d	168 ± 4d	196 ± 4d	224 ± 4d	252± 4d	280 ±4d	308 ±4d	336±4d	364 ± 4d	
C-SSRS[m]	X	X	X	X	X	X	X	X	X	X
Self-Harm Supplement Form[m]	X	X	X	X	X	X	X	X	X	X
FACIT Fatigue Scale					X				X	X
SF-36					X				X	X
ASAS HI					X				X	X
QIDS-SR16					X				X	X
EQ-5D-5L									X	X
WPAI-SpA									X	X
Laboratory Tests										
CRP	X	X	X	X	X	X	X	X	X	X
HBV[r]		X[r]			X[r]		X[r]		X[r]	X[r]
Urine pregnancy test[s]	X	X	X	X	X	X	X	X	X	X
Serum chemistry	X	X	X	X	X		X		X	X
PTT, PT/INR		X			X				X	
Lipid panel (fasting)[t]		X			X				X	
Hematology	X	X	X	X	X		X		X	X
Urinalysis		X			X				X	X
Immunogenicity testing[u]		X			X				X	X
PK sampling[u,v]		X			X				X	X

	Post-Treatment Follow-Up for Patients Discontinuing Treatment (Period 4)[w]	
	Required Follow-Up Visits	
CRF V (visit) number	V801	V802
Study Weeks	LV + 4W	LV + 12W
Study Days	±14d	±14d
Concomitant medications	X	X
Vital signs (BP and pulse)[d]	X	X
Weight[aa]	X	X
Preexisting conditions and medical history[h]	X	X
Adverse events	X	X
C-SSRS[m]	X	X
Self-Harm Supplement Form[m]	X	X
HBV[r]	X[r]	X[r]
Serum chemistry	X	X
Hematology	X	X
Immunogenicity testing[u]	X	X
PK sampling[u,v]	X	X

Abbreviations: AP = anterior posterior; ASAS HI = Assessment of Spondyloarthritis International Society Health Index; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; BASMI = Bath Ankylosing Spondylitis Metrology Index; BP = blood pressure; CRF = case report form; CRP = high sensitivity C-reactive protein; C-SSRS = Columbia–Suicide Severity Rating Scale; d = days; DNA = deoxyribonucleic acid; ECG = electrocardiogram; EQ-5D-5L = European Quality of Life–5 Dimensions–5 Level; ETV = early termination visit; FACIT = functional assessment of chronic illness therapy; FSH = follicle stimulating hormone; HBcAb+ = positive for anti-hepatitis B core antibody; HBsAb = anti-hepatitis B surface antibody; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HLA = human leukocyte antigen; INR = international normalized ratio; IP = investigational product; LV = last visit; MASES = Maastricht Ankylosing Spondylitis Enthesitis Score; MRI = magnetic resonance imaging; NRS = numeric rating scale; NSAID = nonsteroidal anti-inflammatory drug; PK = pharmacokinetic; PPD = purified protein derivative; PT = prothrombin time; PTT = partial thromboplastin time; QIDS-SR16 = Quick Inventory of Depressive Symptomatology-self report (16 items); SDAL = Study Drug Administration Log; SF-36 = Short Form 36; SIJ = sacroiliac joint; SpA = spondyloarthritis; T4 = thyroxine; TB = tuberculosis; TSH = thyroid stimulating hormone; V = study visit; W = study week; WPAI-SpA = Work Productivity Activity Impairment Questionnaire–Spondyloarthritis.

[a] Patient who has received at least 1 dose of IP discontinues from study treatment should complete early termination visit (ETV) and will enter the Post Treatment Follow-Up Period (Period 4) after ETV.

[b] Demographics includes recording of year of birth, gender and ethnicity.

[c] One complete physical examination (excluding pelvic, rectal examination) will be performed at screening. All physical examinations throughout the study must include a symptom-directed physical as well as examination of heart, lungs, abdomen, eyes, and visual examination of the skin.

[d] BP and pulse will always be measured in sitting position and will be recorded before IP dosing at all visits; in addition, BP and pulse will be recorded approximately 1 hour post-dosing at baseline (Week 0) and Week 16 Refer to Section 9.4.2 for more details.

[e] Habits include recording of caffeine, alcohol, and tobacco consumption.

[f] A posterior anterior chest X-ray will be taken locally at screening unless one has been obtained within 3 months of screening (Visit 1) (provided the X-ray and/or report are available for review). Refer to Section 9.4.7 for more details.

[g] Refer to rescreening guidance as appropriate (Section 6.4).

[h] Evaluation includes historical events and preexisting conditions.

[i] Patients need to be asked about presence of eye symptoms; if eye symptoms are present, then an eye examination is required. Refer to Section 9.4.6 for specific instructions.

[j] Refer to Section 7.1.1 for specific IP administration instructions.

[k] IP compliance will be assessed by review of the Study Drug Administration Log, return of empty or unused investigational product packaging, and/or direct questioning

[l] An X-ray of the SIJ will be performed during the Screening Period (Period 1) unless an X-ray taken prior to screening is available for central reading, is of good quality, and confirms diagnosis of r-axSpA. All X-rays require central reading ONLY, regardless of date taken. Central reading will define eligibility using the mNY criteria. If central reading of a preexisting X-ray is not consistent with r-axSpA by central reading, a new X-ray of the SIJ may be taken during Period 1 and sent in for central reading.

[m] A Self-Harm Follow-Up Form is to be completed for each discrete self-harm event identified on the C-SSRS and the Self-Harm Supplement Form.

[n] HLA-B27 test will be performed centrally.

[o] Approval from the Lilly clinical research physician or clinical research scientist must be obtained before a CRP retest is permitted. If the CRP lab is retested, the most recent value will be used for randomization.

[p] If the QuantiFERON®-TB Gold test or T-SPOT® is available, either test may be used instead of the PPD TB test. The QuantiFERON®-TB Gold test may be performed locally or centrally; the T-SPOT® must be performed locally. PPD tests must be read 2-3 days after Visit 1. Refer to Section 9.4.7 for more details.

[q] For female patients ≥40 and <60 years of age who have had a cessation of menses for at least 12 months, an FSH test will be performed to confirm non-childbearing potential (FSH ≥40 mIU/mL or ≥40 IU/L). FSH test will be performed centrally.

[r] All patients will be tested for HBV at screening. Patients that are HBcAb+ at screening, regardless of HBsAb status, will have a serum HBV DNA obtained by the central laboratory. Patients that are found to be HBV DNA positive (detectable) at screening will be excluded from the trial. Patients that are HBV DNA negative (undetectable) may be enrolled into the study with required HBV DNA monitoring every 3 months during treatment and 12 weeks after the last dose of ixekizumab. If the result of the HBV DNA testing is positive, the patient is to be discontinued from the study and is to receive appropriate follow-up medical care (refer to Section 9.4.10.3 for further information regarding the timing of discontinuation).

[s] Only for females of childbearing potential. Serum pregnancy test will be done at Visit 1 only and will be performed centrally. Patients determined to be pregnant will be discontinued from treatment and will no longer be administered IP (see Section 8.1). Patients will undergo urine pregnancy testing at the clinic during scheduled visits through Week 52. Additional urine pregnancy testing can be performed at the investigator's discretion. If required per local regulations, testing can occur at other intervals during the study treatment period and/or follow-up period.

[t] For the fasting lipid profile, patients are not to eat or drink anything except water for 12 hours prior to test.

[u] Immunogenicity samples may also be analyzed for ixekizumab serum concentration to facilitate in the interpretation of immunogenicity data. An additional blood sample will be collected, when possible, for any patient who experiences a potential systemic allergic/hypersensitivity reaction during the study as judged by the investigator.

[v] PK samples are to be collected before IP injection.

[w] Patients receiving IP who discontinue at any time prior to the end of the study or who complete the study (Week 52) will have safety Follow-Up Visits 801 and 802 at 4 and 12 weeks, respectively, after the date of their last visit.

[x] If MRI is conducted on the same day as study visit, ensure that any scales/questionnaires are completed prior to administering any premedication to facilitate patient undergoing an MRI (for example, morphine or equivalent for significant pain as judged by the investigator or a benzodiazepine for claustrophobia).

[y] For all patients, screening MRIs of the spine must be completed ≤30 days prior to randomization.

[z] The Week 16 MRI may be collected up to 10 days **prior** to Week 16 (Visit 8). The Week 16 MRI must be collected prior to the Week 16 (Visit 8) dosing. For ETV, MRI requirements are dependent on the timing of study discontinuation. If discontinuation is:

- at or before Visit 5, no MRI is required at ETV.
- after Visit 5 up to and including Visit 8 (Week 16), MRI is required at ETV.

- after Visit 8, repeat MRI is required only if ETV occurs on or after Visit 12.

[aa] Weight is only captured on eCRF at V2, V8, V10, V17, and/or ETV. Body weight collected at other visits is used only for calculation of creatinine clearance.

[bb] The Week 52 MRI may be collected up to 10 days prior to Week 52 (Visit 17).

[cc] Cervical and lumbar spine only; serves to evaluate presence of total ankylosis at screening (Refer to Section 6.2, exclusion criterion [10]). X-ray of the spine does not need to be repeated if one is available that was taken ≤3 months prior to screening (Visit 1; refer to Sections 6.2, and 6.4) and has passed quality assessment by central reading vendor.

3. Introduction

3.1. Study Rationale

Eli Lilly and Company (hereafter Lilly) is investigating ixekizumab as a treatment option for radiographic axial spondyloarthritis (r-axSpA) based on its mechanism of action (MoA), selectively blocking interleukin-17A (detailed in the Investigator's Brochure [IB]). The following subcutaneous (SC) ixekizumab treatment regimen of 80 mg every 4 weeks (Q4W) with a starting dose of 160 mg (at Week 0) will be studied in this trial. Wide range of dosing regimens were evaluated in Phase 2 psoriasis and rheumatoid arthritis (RA) studies and demonstrated efficacy. Ixekizumab 80 mg Q2W and Q4W treatment regimens with a 160 mg starting dose were evaluated in pivotal Phase 3 studies in psoriasis and psoriatic arthritis (PsA) and demonstrated efficacy, with a favorable benefit/risk profile (Gottlieb et al. 2015; Griffiths et al. 2015; Mease et al. 2015). Recently disclosed data from phase 3 studies of both ixekizumab Q2W and Q4W have recently demonstrated the efficacy of blocking IL-17A in the treatment of r-axSpA in biological disease-modifying antirheumatic drug (bDMARD)-naïve as well as in tumor necrosis factor (TNF) inhibitor experienced patients (van der Heijde et al. 2018; Deodhar et al. 2019b).

3.2. Background

Axial spondyloarthritis (axSpA) is a chronic inflammatory disease predominantly affecting the axial skeleton (sacroiliac joints [SIJ] and spine) (Poddubnyy 2013). Axial spondyloarthritis is now recognized as a single disease entity, with a subset defined by the presence of radiographically defined structural damage of the SIJ (r-axSpA) and a subset without clear structural damage defined radiographically (nr-axSpA). When comparing axSpA with RA, it can be noted that while RA can be divided into erosive and nonerosive or seropositive and seronegative subsets, it is well accepted that it is still one disease. Axial spondyloarthritis, in a similar fashion, also has subsets, and thus can be considered a single disease (Deodhar et al. 2014).

Radiographic axSpA (r-axSpA), formerly called ankylosing spondylitis (AS), represents a disease in which there is evidence of disease features on radiographic imaging. It is a chronic inflammatory disease characterized by chronic inflammation of the axial and SIJ and variable involvement of the peripheral joints (Braun and Sieper 2007). As the disease progresses, it can lead to new bone formation in the form of syndesmophytes and joint ankylosis, primarily in the axial skeleton. Patients with r-axSpA may also have extra-articular manifestations of the disease such as enthesitis, anterior uveitis, psoriasis, and inflammatory bowel disease, as well as comorbidities of aortitis or cardiac conduction abnormalities. Compared with the general population, patients with r-axSpA have increased rates of work disability, unemployment, and mortality (Boonen and van der Linden 2006).

Axial spondyloarthritis affects up to 1.4% of the adult population worldwide (Braun and Sieper 2007; Reveille et al. 2012; Strand et al. 2013). Although the exact etiology is unknown, it has been indicated that genetic factors and several loci are likely to be involved in susceptibility to the disease (Reveille 2011). There is a strong association with the major histocompatibility

complex, human leukocyte antigen (HLA)-B27. Up to 90% to 95% of patients with r-axSpA are positive for HLA-B27, and the risk of this disease developing is as high as about 5% in HLA-B27-positive individuals and substantially higher in HLA-B27-positive relatives of patients (Braun and Sieper 2007). Most of the other known genetic susceptibility comes from genes involved in cytokine production, specifically including genes in the T helper (Th)17 pathway (Maksymowych 2010; Reveille 2011).

Current standard of care for r-axSpA includes regular exercise, physical therapy, nonsteroidal anti-inflammatory drugs (NSAIDs), and TNF alpha inhibitors (Braun et al. 2011; Ward et al. 2015). Corticosteroid injections may also be of some benefit. Though NSAIDs are the first line of drug treatment for axSpA, they are not effective or well tolerated in all patients (Braun and Sieper 2009). In contrast to patients with RA, patients with axSpA do not respond well to conventional disease-modifying antirheumatic drugs (cDMARDs) including methotrexate (MTX) or systemic corticosteroids (Braun and Sieper 2009; Haibel and Specker 2009).

TNF inhibitors are effective and frequently prescribed when NSAID treatment has failed or cannot be tolerated (Zochling et al. 2006). While TNF inhibitors have proven to be effective treatments for axSpA, an unmet need remains, as not all patients respond well to or tolerate TNF inhibitor treatments (van der Heijde et al. 2006; Heiberg et al. 2008; Inman et al. 2008; Glintborg et al. 2010). While TNF inhibitors have demonstrated significant impact on signs and symptoms, function, and quality of life, they have not been able to demonstrate significant effect on structural progression in prospective clinical studies. The use of these biologic therapies in various diseases also is associated with safety concerns, such as opportunistic infections, demyelinating disorders, blood dyscrasias, reactivation of tuberculosis (TB), and exacerbation of congestive heart failure (Moreland 2005; Smith et al. 2009). There remains, therefore, a significant unmet need for safer, more effective treatments for patients with axSpA (Dougados and Baeten 2011). Ixekizumab may offer an alternative treatment approach to TNF inhibitor therapy in patients with axSpA.

Ixekizumab (LY2439821) is a humanized immunoglobulin G subclass 4 (IgG4) monoclonal antibody (MAb) that neutralizes the cytokine interleukin-17A (IL-17A, also known as IL-17). Ixekizumab treatment is administered by SC injections. Compelling scientific information exists to date suggesting an important role of the IL-23/IL-17 pathway in the pathogenesis of axSpA (Baeten et al. 2010, 2014a; Maksymowych 2010; Baraliakos et al. 2011; Reveille 2011; Yeremenko et al. 2014). The demonstration of increased IL-17 producing Th17 lymphocyte numbers and serum IL-17 levels in r-axSpA is consistent with a direct role of Th17 lymphocytes in this disease (Wendling et al. 2007; Jandus et al. 2008; Mei et al. 2011). IL-17 secreting cells have also been detected in situ in the bone marrow of facet joints obtained from patients with r-axSpA (Appel et al. 2008).

Selectively targeting IL-17A with ixekizumab is hypothesized to provide therapeutic benefit without unduly impacting host defenses. As such, ixekizumab may offer a therapeutic option for patients who are candidates for initial systemic treatment as well as those patients who have lost response, failed to respond, or are intolerant to currently marketed drugs, and may also offer a more favorable safety profile compared to currently marketed therapies.

3.3. Benefit/Risk Assessment

More information about the known and expected benefits, risks, serious adverse events (SAEs) and reasonably anticipated adverse events (AEs) of ixekizumab are to be found in the IB.

4. Objectives and Endpoints

Table RHCH.1 shows the objectives and endpoints of the study.

Table RHCH.1. Objectives and Endpoints

Objectives	Endpoints
Primary • The primary objective is to compare ixekizumab 80 mg Q4W versus placebo in bDMARD-naïve patients with active r-axSpA at Week 16	• Proportion of patients achieving an Assessment of Spondyloarthritis International Society 40 (ASAS40) response
Secondary **The major secondary objectives are:** • To compare ixekizumab 80 mg Q4W to placebo in overall study population at Week 16	• Proportion of patients achieving an ASAS40 response • Proportion of patients achieving an ASAS20 response • Change from baseline in Ankylosing Spondylitis Disease Activity Score (ASDAS) • Change from baseline in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) • Change from baseline in Bath Ankylosing Spondylitis Functional Index (BASFI) • Proportion of patients achieving ASDAS < 2.1 • Change from baseline in magnetic resonance imaging (MRI) of the spine (Spondyloarthritis Research Consortium of Canada [SPARCC] score) • Change from baseline in Short Form 36 (SF-36) physical component score (PCS)

Other secondary objectives are:
• To compare ixekizumab regimen 80 mg Q4W to placebo during the 16-week placebo-controlled period (Period 2) in overall study population
	• Proportion of patients who achieve ASAS20, ASAS40, ASAS 5/6, and partial remission by ASAS criteria
	• Change from baseline in the individual components of the ASAS criteria
	• Change from baseline in BASDAI
	• Proportion of patients reaching BASDAI50
	• Change from baseline in ASDAS
	• Proportion of patients who experience clinically-important improvement (change of ASDAS from baseline ≥1.1) or major improvement (change of ASDAS from baseline ≥2.0 or achievement of the lowest possible score) or inactive disease (ASDAS score <1.3)
	• Change from baseline in the measure of high sensitivity C-reactive protein (CRP)
	• Change from baseline in BASFI
	• Change from baseline in mobility
	  ○ Bath Ankylosing Spondylitis Metrology Index (BASMI) (linear) and individual components
	  ○ Chest expansion
	  ○ Change from baseline in occiput to wall distance

	• Change from baseline in MRI of the SIJ (SPARCC score) • Change from baseline in Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) • Incidence rate of anterior uveitis or uveitis flares • Change from baseline in the following health outcomes measures: Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue Scale, Work Productivity Activity Impairment–Spondyloarthritis (WPAI-SpA) scores, and SF-36 (both PCS and mental component scores [MCS]) and Quick Inventory of Depressive Symptomatology–Self Report 16 items (QIDS-SR16) score
• To determine if the effect of ixekizumab is maintained through Week 52	All endpoints assessed at Week 16 (above) and during the 16-week placebo-controlled period (above) will continue to be assessed through Week 52. In addition, the following endpoint is added: • NSAID intake (ASAS-NSAID score and % of patients taking NSAIDs)
• To measure ixekizumab exposure and assess the relationship between exposure and immunogenicity	• Serum trough concentrations of ixekizumab • Ixekizumab serum trough concentrations associated with ADA titer sub groups
Exploratory • To evaluate time to first response	• Onset of action and treatment response (ASAS, ASDAS, CRP, BASFI) during the placebo-controlled period
• To compare ixekizumab regimen 80 mg Q4W to placebo during the 16-week placebo-controlled period (Period 2)	• Change from baseline in SPARCC SIJ Structural Score (SSS) • Change from baseline in ASAS HI score
• To evaluate the incidence of anti-ixekizumab antibodies and their relationship to the efficacy of ixekizumab	• Efficacy response rates listed below at Weeks 16 and 52 by treatment-emergent anti-drug antibody (TE-ADA) status and by neutralizing anti-drug antibody (NAb) status: o Proportion of patients achieving ASAS40 o Proportion of patients achieving ASAS20 o Proportion of patients achieving ASDAS inactive disease
Note: Other exploratory objectives and endpoints will be specified in the statistical analysis plan (SAP).	

5. Study Design

5.1. Overall Design

Study I1F-MC-RHCH (RHCH) is a Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group, outpatient study to evaluate the efficacy and safety of ixekizumab 80 mg Q4W SC with starting dose of 160 mg at Week 0 as compared to placebo SC in patients with r-axSpA, during a 16-week Blinded Treatment Dosing Period.

Study RHCH will also evaluate long-term efficacy and safety of ixekizumab during the Extended Treatment Period (Period 3) for a total treatment duration of 1 year (52 weeks).

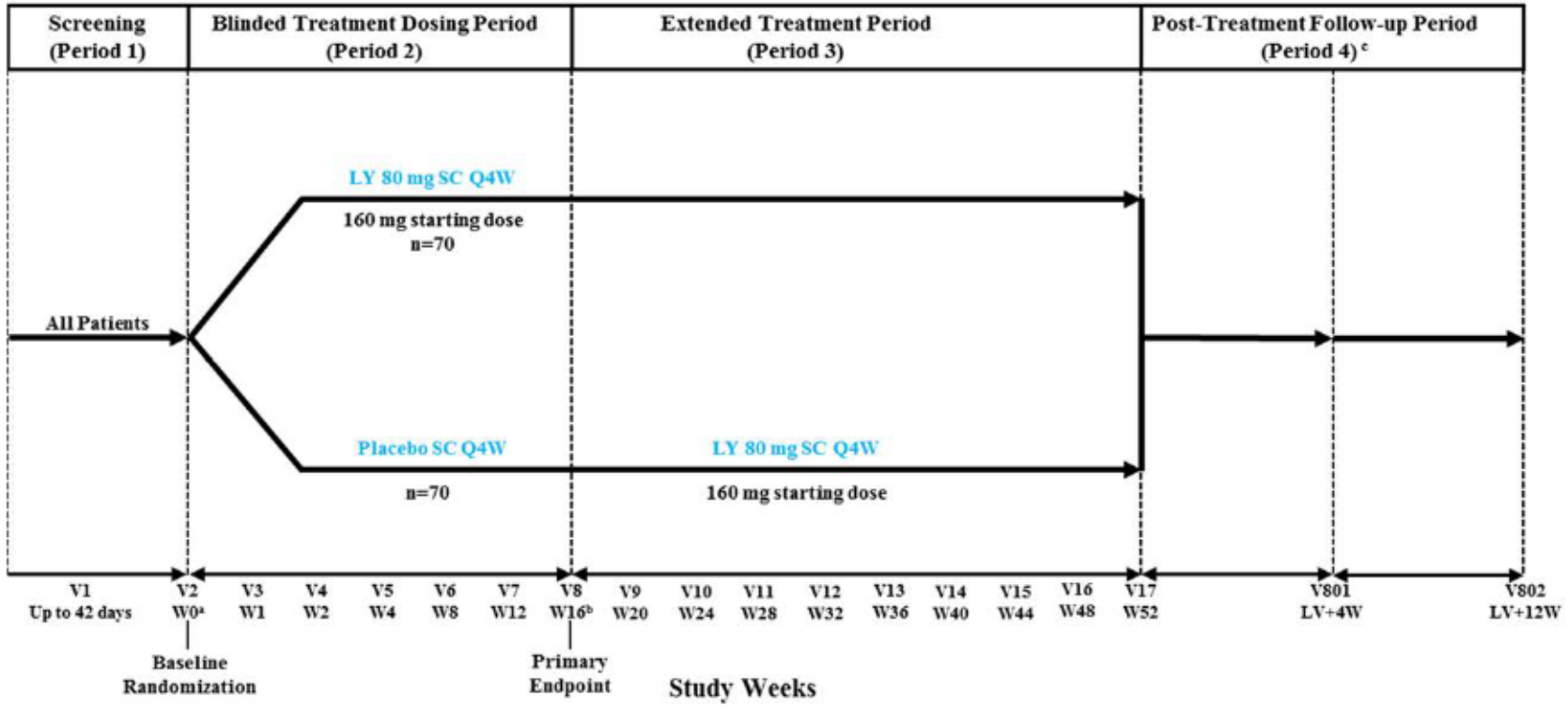
Figure RHCH.1 illustrates the study design; both treatment groups and administration of the investigational product are described in Section 7.1; and the Study Drug Administration Log is described in Section 7.2.1.

All procedures to be conducted during the study, including timing of all procedures, are indicated in the Schedule of Activities (Section 2). Selected study procedures are to be performed prior to administration of the investigational product, as applicable. Appendix 2 lists the specific laboratory tests that will be performed for this study. Patients discontinuing from study treatment who have received at least 1 dose of investigational product will continue to the early termination visit (ETV) prior to proceeding to the Post-Treatment Follow-Up Period. For the management of patient safety, all patients are to be monitored through the Post-Treatment Follow-Up Period at least as frequently as indicated in the Schedule of Activities (Section 2).

Excluded and concomitant medications are detailed in Section 7.7.

Pharmacokinetic (PK) sampling is detailed in Section 9.5.

Figure RHCH.1 illustrates the study design.



Abbreviations: LV = last visit; LY = ixekizumab; n = number of patients; Q4W = every 4 weeks; SC = subcutaneous; V = study visit; W = study week.

a All patients will receive 2 injections at baseline, as detailed in Section 7.1. Patients randomized to the ixekizumab regimen will receive a 160 mg starting dose.

b All patients will receive 2 injections at Week 16, as detailed in Section 7.1. Patients randomized to placebo at Week 0 will begin ixekizumab 80 mg Q4W at Week 16 with a 160 mg starting dose, and patients randomized to ixekizumab at Week 0 will receive 1 ixekizumab 80 mg injection and 1 placebo injection at Week 16 to maintain the blinding (Section 7.1).

c Patients who discontinue from study treatment for any reason and who have received at least 1 dose of investigational product will continue to the early termination visit (ETV) before entering the Post-Treatment Follow-Up Period. V801 and V802 are required for all patients (Section 9.4.10).

Figure RHCH.1. Illustration of study design for Clinical Protocol I1F-MC-RHCH.

5.2. Number of Participants

Participants will be screened to achieve 140 randomized participants for an estimated total of 70 evaluable participants per treatment group.

5.3. End of Study Definition

End of the study is the date of the last visit or last scheduled procedure shown in the Schedule of Activities (Section 2) for the last patient in the trial.

5.4. Scientific Rationale for Study Design

Ixekizumab 80 mg Q4W with a 160 mg starting dose will be studied as detailed in Section 7.1. Dose justification is outlined in Section 5.5. The study blind is maintained as described in Section 7.3.

The placebo-controlled Blinded Treatment Dosing Period (Period 2) is designed to minimize bias in the evaluation of ixekizumab in patients with r-axSpA for both efficacy and safety. All patients may still receive treatment in the form of the allowed concomitant medications as described in the study inclusion and exclusion criteria (Sections 6.1 and 6.2) and concomitant therapy (Section 7.7). Patients can be discontinued from study treatment at any time by investigator or patient decision if they are considered to be receiving insufficient benefit from study treatment (Section 8.1).

As of Week 16 (after completion of Period 2), investigators are allowed to adjust some concomitant medications, if needed, as specified in Section 7.7, across all treatment groups.

Patients originally assigned to placebo during Period 2 will receive ixekizumab 80 mg Q4W with a 160 mg starting dose at Week 16.

Ixekizumab 80 mg Q4W is continued beyond Week 16 to further assess safety and efficacy during the Extended Treatment Period (Period 3).

The effectiveness of ixekizumab in treating r-axSpA will be assessed primarily by the ASAS40 response rate in bDMARD-naïve patients at Week 16. ASAS 40 and ASAS20 response will also be assessed in overall study population at Week 16. These measures and the Week 16 endpoint are in alignment with efficacy endpoints for currently approved r-axSpA therapies and with regulatory guidance (EMA 2009). Steady state exposure of ixekizumab is expected to be reached by Week 16. Based on previous studies with ixekizumab in patients with psoriasis, RA, PsA and r-axSpA, maximum or near maximum clinical effect in r-axSpA were achieved within this time frame for ixekizumab treatment (Griffiths et al. 2015; Genovese et al. 2016; Mease el al. 2017; Nash et al. 2017; van der Heijde et al. 2018; Deodhar et al. 2019b).

Baseline C-reactive protein (CRP) has been reported as a predictor of response in patients with r-axSpA treated with TNF inhibitors (Inman et al. 2008; de Vries et al. 2009; Sieper et al. 2011; Vastesaeger et al. 2011); hence, by including it as a stratification factor, it ensures balance in baseline CRP levels, resulting in greater comparability across treatment groups at baseline. Similarly, the prior TNF inhibitors used has been reported to potentially impact response rates of

subsequently used biologics (Lie et al. 2011; Glintborg et al. 2013); therefore, patients will also be stratified based on prior TNF inhibitor experienced or biological naïve. Thus baseline status will produce the following 3 strata:

1) AS patients who are biologic naïve and have normal baseline CRP.

2) AS patients who are biologic naïve and have elevated baseline CRP.

3) AS patients who have demonstrated either intolerance or inadequate response to one TNF inhibitor and have elevated baseline CRP.

The Extended Treatment Period (Period 3) will permit collection of data for the assessments of maintenance of efficacy and long-term safety with ixekizumab.

The Post-Treatment Follow-Up Period (Period 4) is important for safety and efficacy monitoring following administration of the last study treatment.

5.5. Justification for Dose

The treatment regimen to be evaluated in this study (ixekizumab 80 mg Q4W with a starting dose of 160 mg administered subcutaneously) was selected based on clinical and PK/pharmacodynamic (PD) data from psoriasis, RA and r-axSpA studies.

Extensive dose-ranging studies were conducted in psoriasis and RA populations, exploring multiple doses of ixekizumab in both indications. The dose-ranging study in RA included 2 different patient populations (bDMARD-naïve and TNF-inadequate responders) (Genovese et al. 2014.

Finally, the efficacy of common treatment regimens of other therapies (most TNF inhibitors and secukinumab) has been demonstrated across various rheumatological conditions (RA, PsA, axSpA) (Simponi® package insert, 2015; 2015 package inserts for Cimzia®, Cosentyx®, Enbrel®, and Humira®; Sanford and McKeage 2015).

Collectively, these current internal (ixekizumab) and external (TNF inhibitors and secukinumab) scientific data support the rationale for studying ixekizumab in patients with r-axSpA with the proposed treatment regimen of ixekizumab 80 mg Q4W with a starting dose of 160 mg.

6. Study Population

The study population will include patients with a prior physician diagnosis of axSpA who fulfill protocol criteria for active r-axSpA (with sacroiliitis defined radiographically according to the modified New York [mNY] criteria, based on central reading, associated with at least 1 SpA feature and [Appendix 5]), who have given written informed consent.

Study investigator(s) will review patient history and screening test results from Visit 1 (all criteria), and Visit 2 as per the Schedule of Activities (Section 2) to determine if the patient meets all inclusion and none of the exclusion criteria to qualify for participation in the study. All screening activities must be completed and reviewed before the patient is randomized. Patients may be rescreened in the circumstances described in Section 6.4.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, are not permitted.

In this protocol section, the following definitions apply:

- Screening is defined as Visit 1, up to 42 days prior to baseline randomization.
- Baseline randomization visit is defined as Visit 2 (Week 0).

6.1. Inclusion Criteria

Patients are eligible to be included in the study only if they meet all of the following criteria at screening or as specified:

Type of Patient and Disease Characteristics

[1] Have an established diagnosis of r-axSpA with sacroiliitis defined radiographically according to the mNY criteria (van der Linden et al. 1984) based on central reading: sacroiliitis grade ≥2 bilaterally or grades 3 to 4 unilaterally.

AND

At least 1 SpA feature, according to ASAS criteria (Rudwaleit et al. 2009; Sieper et al. 2009), listed in Appendix 5.

[2] Patients have a history of chronic back pain ≥3 months with age at onset <45 years.

[3] Have active r-axSpA defined as BASDAI ≥4 and total back pain ≥4 (Sieper et al. 2009, Box 25 Spinal Pain) on an NRS at screening and baseline.

[4] Biologic naïve or have had prior treatment with 1 TNF inhibitor. The TNF inhibitor experienced patient must have discontinued TNF inhibitor due to either intolerance or an inadequate response and have elevated baseline CRP (defined as: In the opinion of the investigator, the patient had an inadequate response to at least 12 weeks of treatment with a TNF inhibitor at an adequate dose and baseline CRP > 5.00mg/L). Biologic naïve patient would be enrolled regardless of the CRP level.

Note: The following washout periods prior to baseline randomization must be followed: etanercept ≥28 days; infliximab, adalimumab, or certolizumab pegol ≥60 days; golimumab ≥90 days.

[5] Must have had an inadequate response, as determined by the investigator, to 2 or more NSAIDs at the therapeutic dose range for a total duration of at least 4 weeks OR have a history of discontinuation due to intolerance to ≥2 NSAIDs.

[6] Patients must have a history of prior therapy for axSpA of at least 12 weeks prior to screening. Examples of prior therapy may include but are not limited to physical therapy, NSAID, and TNF inhibitor treatment.

[7] If taking NSAIDs or cyclooxygenase-2 (COX-2) inhibitors, the dose must be stable for at least 2 weeks prior to baseline randomization.

Patient Characteristics

[8] Are ambulatory male or female patients ≥18 years of age at time of screening.

[9] Must agree to use a reliable method of birth control:

- If a male patient, patient agrees to use a reliable method of birth control during the study and for at least 12 weeks following the last dose of investigational product, whichever is longer. Methods of birth control include, but are not limited to, condoms with spermicide and male sterilization.

OR

- If a female patient is a woman of childbearing potential who tests negative for pregnancy and agrees to use a reliable method of birth control or remain abstinent during the study and for at least 12 weeks following the last dose of investigational product, whichever is longer. Methods of contraception include, but are not limited to: oral contraceptives, contraceptive patch, injectable or implantable contraceptives, intrauterine device, vaginal ring, diaphragm with contraceptive gel, or condom with contraceptive foam.

OR

- If a female patient is a woman of nonchildbearing potential, she must test negative for pregnancy and is not required to use any method of birth control. Nonchildbearing potential is defined as:

  Women who have had surgical sterilization (hysterectomy or bilateral oophorectomy or tubal ligation)

  - or

  Women who are ≥60 years of age

  - or

Women ≥40 and <60 years of age who have had a cessation of menses for ≥12 months and a follicle stimulating hormone (FSH) test confirming nonchildbearing potential (≥40 mIU/mL or ≥40 IU/L).

Informed Consent

[10] Have given written informed consent approved by Lilly, or its designee, and the Investigational Review Board (IRB)/Ethical Review Board (ERB) governing the site.

6.2. Exclusion Criteria

Patients will be excluded from study enrollment if they meet any of the following criteria at screening or as specified:

Medical Conditions

[11] Have total ankylosis of the spine, as assessed locally, based on lateral radiographs of the cervical and lumbar spine.

[12] Have a history of other systemic inflammatory diseases (such as but not limited to: lupus, vasculitis or RA), or other chronic pain conditions (such as but not limited to fibromyalgia) that might confound the evaluations of benefit from ixekizumab therapy.

Note: Patients with psoriasis that have never received and do not require systemic treatment for psoriasis, such as but not limited to oral agents or biologic therapies, can be included provided these patients fulfill the entry criteria.

[13] Have active Crohn's disease (CD) or active ulcerative colitis (UC).

Note: Patients may be enrolled if they have had a history of inflammatory bowel disease (IBD), including CD and UC, but have had no exacerbation for ≥6 months prior to baseline randomization and, if currently on treatment, must be on stable treatment for ≥6 months prior to baseline randomization.

[14] Have evidence of active anterior uveitis (an acute episode) within the last 4 weeks prior to baseline randomization.
Note: These patients may be rescreened only one time ≥4 weeks after resolution of acute symptoms.

[15] Have current or a history of lymphoproliferative disease, or signs or symptoms of lymphoproliferative disease within 5 years prior to baseline randomization; or have active or history of malignant disease within 5 years prior to baseline randomization.

[16] Have a history of fluid overload, myocardial infarction (MI), uncompensated heart failure, or evidence of new-onset ischemic heart disease or in the opinion of the investigator other serious cardiac disease, within 12 weeks prior to baseline randomization.

[17] Presence of significant uncontrolled cerebrocardiovascular events (for example, unstable angina, unstable arterial hypertension, moderate-to-severe heart failure [New York Heart Association class III/IV], or cerebrovascular accident) at screening that, in the opinion of the investigator, pose an unacceptable risk to the patient if participating in the study or of interfering with the interpretation of data.

[18] Presence of any comorbid respiratory, hepatic, renal, gastrointestinal, endocrine, hematologic disorders, at screening that, in the opinion of the investigator, pose an unacceptable risk to the patient if participating in the study or of interfering with the interpretation of data.

[19] Presence of any neurologic or neuropsychiatric disorders, at screening that, in the opinion of the investigator, poses an unacceptable risk to the patient if participating in the study or of interfering with the interpretation of data.

[20] Presence of significant uncontrolled neuropsychiatric disorder; have recent history (within 30 days prior to screening visit [Visit 1] and any time between screening visit [Visit 1] and baseline randomization [Visit 2]) of a suicide attempt; or have a score of 3 on Item 12 (Thoughts of Death or Suicide) of the Quick Inventory of Depressive Symptomatology-self report (16 items) (QIDS-SR16) at screening or baseline randomization or are clinically judged by the investigator to be at risk for suicide.

[21] Have presence or personal history or family history (1st degree relative) of demyelinating disorder.

Note: 1st degree means child, parent, or sibling, provided a blood relationship exists.

[22] Patients who have:

- in the past 12 weeks prior to baseline randomization:
  - had a serious infection (for example, pneumonia, cellulitis),
  - have been hospitalized for an infection,
  - or have received intravenous (IV) antibiotics for an infection,
- or in the past 24 weeks prior to baseline randomization had a serious bone or joint infection
- or have ever had,
  - an infection of an artificial joint,
  - an infection that occurs with increased incidence in an immunocompromised host (including, but not limited to, Pneumocystis jirovecii pneumonia, symptomatic histoplasmosis, or coccidioidomycosis)

[23] Have a known immunodeficiency or are immunocompromised to an extent such that participation in the study would pose an unacceptable risk to the patient.

[24] Have or had a herpes zoster or any other clinically apparent varicella-zoster virus infection within 12 weeks of baseline randomization.

[25] Have any other active or recent infection within 4 weeks of baseline randomization that in the opinion of the investigator, would pose an unacceptable risk to the patient if participating in the study.

Note: These patients may be rescreened one time ≥4 weeks after resolution of symptoms.

[26] Have a known allergy or hypersensitivity to any biologic therapy that would pose an unacceptable risk to the patient if participating in this study.

[27] Have had surgical treatment of a joint that is to be assessed in the study within 8 weeks prior to baseline randomization or will require surgical treatment of a joint that is to be assessed in the study during the first 16 weeks of the trial.

[28] Have had any major surgery within 8 weeks prior to baseline randomization, or will require major surgery during the study that in the opinion of the investigator and in consultation with Lilly or its designee would pose an unacceptable risk to the patient.

Prior/Concurrent Therapy or Clinical Trial Experience

[29] Have received cDMARDs and/or other therapies such as but not limited to: gold salts, cyclosporine, azathioprine, dapsone, 6-mercaptopurine, mycophenolate mofetil, or any other immunosuppressive agents within 4 weeks prior to baseline randomization.

Exception: MTX (oral or parenteral up to 25 mg/week), sulfasalazine (up to 3 g/day), or hydroxychloroquine (up to 400 mg/day) may be allowed IF at stable dose for at least 4 weeks prior to baseline randomization.
AND
if used, must not be in any combination with other cDMARDs.

Note: If MTX is used, local standard of care is to be followed for concomitant administration of folic or folinic acid with MTX.

[30] Use of oral corticosteroids >10 mg/day prednisone or its equivalent.

Note: If patients are taking prednisone or its equivalent and the dose is ≤10 mg/day, the dose must be stable for at least 4 weeks prior to baseline randomization.

[31] Have received any prior, or are currently receiving, treatment with biologic or other immunomodulatory agents, including investigational therapies (such as but not limited to Janus kinase (JAK) inhibitors, IL-1, IL-6 , IL-23 , IL-17 (including ixekizumab), IL-17R, T cell, or B cell targeted therapies).
Note: Previous TNF inhibitor therapy is permitted.

[32] Are currently enrolled in, have participated, or discontinued from a clinical trial involving an investigational product or nonapproved use of a drug or device within the last 30 days prior to screening or a period of at least 5 half-lives of the last administration of the drug, whichever is longer.

Note: Investigational products that are biologic or other immunomodulatory agents are not permitted regardless of washout period (described in criterion above).

[33] Are currently enrolled in any other clinical study involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study.

[34] Are currently receiving or have received treatment with denosumab within 6 months prior to baseline randomization.

[35] Have received any parenteral glucocorticoid administered by intra-articular, intramuscular, or IV injection within 6 weeks prior to baseline randomization, or for whom a parenteral injection of glucocorticosteroids is anticipated during the Blinded Treatment Dosing Period (Period 2) of the study.

[36] Are currently receiving or have received any traditional Chinese medicine (TCM) within 4 weeks prior to baseline randomization.

[37] Use of any opiate analgesic at average daily doses >30 mg/day of morphine or its equivalent or use of variable doses of any opiate analgesic within 6 weeks prior to baseline randomization. Exception for patients with pain that may interfere with undergoing an MRI: patient may receive premedication of ≤30 mg of morphine or equivalent, on the day of the MRI, for significant pain as judged by the investigator.

[38] Had a live vaccination within 12 weeks prior to baseline randomization, or intend to have a live vaccination during the course of the study, or within 12 weeks of completing treatment in this study, or have participated in a vaccine clinical study within 12 weeks prior to baseline randomization. Investigators are to review the vaccination status of their patients and follow the local guidelines for adult vaccination with nonlive vaccines intended to prevent infectious disease prior to therapy.

Note: Killed/inactive or subunit vaccines are expected to be safe; however, their efficacy with concomitant ixekizumab treatment is unknown.

[39] Had a vaccination with Bacillus Calmette-Guérin (BCG) within 12 months prior to baseline randomization, or intend to have this vaccination with BCG during the course of the study, or within 12 months of completing treatment in this study.

Diagnostics Assessments

[40] Have a body temperature ≥38°C (100.5°F) at baseline randomization.

Note: These patients may be rescreened one time ≥4 weeks after documented resolution of elevated temperature.

[41] Have evidence or suspicion of active or latent TB (refer to Section 6.4 for rescreening and Section 9.4.7 for details on determining full TB exclusion criterion).

[42] Are positive for human immunodeficiency virus serology (HIV); that is, positive for human immunodeficiency virus antibody (HIVAb).

[43] Have evidence of or test positive for hepatitis B virus (HBV) by testing positive for: 1) HBV surface antigen (HBsAg+), OR 2) anti-hepatitis B core antibody positive (HBcAb+) and HBV DNA are positive.

Note: Patients who are HBcAb+ and HBV DNA negative may be enrolled in the study. Patients who meet these criteria at screening will be identified by the central laboratory and monitored during the study as detailed in Section 9.4.10.2.

[44] Have evidence of or test positive for hepatitis C virus (HCV). A positive test for HCV is defined as: 1) positive for hepatitis C antibody (anti–HCV Ab); and 2) positive via a confirmatory test for HCV (for example, HCV-polymerase chain reaction).

[45] Have electrocardiogram (ECG) abnormalities that are considered clinically significant and would pose an unacceptable risk to the patient if participating in the study.

[46] Patients having contraindications to MRI (for example, claustrophobia, pacemakers, aneurysm clips, intraocular metallic fragments).

Note: For claustrophobia, premedication with benzodiazepine is allowed (investigator should assess for potential interactions with other concomitant medication(s) such as opiates).

Laboratory tests may not be repeated unless there is a technical error or clinical reason to believe a result may need to be retested within the screening period. Laboratory tests can be repeated a maximum of 1 time, and results must be received and reviewed prior to randomization. For eligibility, the most recent lab panel must not meet any of the following criteria:

[47] At screening, have a neutrophil count <1500 cells/μL (<1.50x10^3/μL or <1.50 GI/L).

[48] At screening, have a lymphocyte count <800 cells/μL (<0.80x10^3/μL or <0.80 GI/L).

[49] At screening, have a platelet count <100,000 cells/μL (<100x10^3/μL or <100 GI/L).

[50] At screening, have aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2.5 times the upper limit of normal (>2.5xULN).

[51] At screening, have a total white blood cell (WBC) count <3000 cells/μL (<3.00x10^3/μL or <3.00 GI/L).

[52] At screening, have hemoglobin <8.5 g/dL (85.0 g/L) for male patients and <8.0 g/dL (80 g/L) for female patients.

[53] Have other clinical laboratory test results at screening that are outside the normal reference range for the population and are considered clinically significant, per investigator assessment.

Other Exclusions

[54] Have donated blood >450 mL within the last 4 weeks prior to screening, or intend to donate blood during the course of the study.

Note: Patients who have donated blood may be rescreened one time ≥4 weeks have passed since initial screening.

[55] Are women who are lactating or breastfeeding.

[56] Are investigator site personnel directly affiliated with this study and/or their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.

[57] Are Lilly employees or its designee or are employees of third-party organizations involved in the study.

[58] Are unwilling or unable to comply with the use of a data collection device to directly record data from the patient.

[59] Have any other condition that precludes the patient from following and completing the protocol, in the opinion of the investigator.

6.3. Lifestyle Restrictions

Not applicable.

6.4. Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened in the following circumstances: patients who test positive for latent TB at screening may be rescreened following appropriate treatment as described in Section 9.4.7; patients who do not qualify at screening under Exclusion Criteria [25], [40], or [54], may be rescreened one time, ≥4 weeks after documented resolution of symptoms or from time of blood donation.

Screening MRIs must be performed ≤30 days prior to baseline randomization (Visit 2). After consultation with Lilly medical, patients may be rescreened if screening MRI(s) of the spine and/or SIJ were performed >30 days prior to baseline randomization.

If a patient is unable to complete all screening procedures within the screening period, the patient may be rescreened after consultation with Lilly medical.

When rescreening is performed, the individual must sign a new informed consent form (ICF) and will be assigned a new identification number. To ensure all eligibility criteria are met, all screening procedures must be repeated unless previously conducted within timeframes specified in the Schedule of Activities (Section 2).

7. Treatments

7.1. Treatments Administered

The Blinded Treatment Dosing Period (Period 2) involves a comparison of ixekizumab 80 mg Q4W to placebo. Ixekizumab treatment regimen will include patients receiving a 160 mg starting dose. All doses are administered via SC injection. Table RHCH.2 shows the treatment regimens.

At baseline (Week 0), all patients will be randomized to a treatment regimen and receive 2 injections. Patients assigned to ixekizumab treatment regimen with 160 mg ixekizumab starting dose will receive 160 mg of ixekizumab as 2 SC injections. Patients assigned to the placebo treatment group will receive 2 SC injections of placebo. During the remainder of the Blinded Treatment Dosing Period (Period 2; Week 0 to Week 16), all patients will receive 1 injection every 4 weeks. Details are provided in Table RHCH.2.

During the Extended Treatment Period (Period 3; Week 16 to Week 52), patients originally assigned to ixekizumab treatment will remain on the same treatment regimen through Period 3. At Week 16, patients originally assigned to placebo will receive ixekizumab 80 mg Q4W with a 160 mg starting dose (as two 80 mg SC injections). To maintain the blind, all patients, regardless of treatment group, will receive 2 SC injections at Week 16. All patients will receive open-label investigational product starting from Week 20.

The investigator or his/her designee is responsible for the following:

- explaining the correct use of the investigational product to the patient/patient caregiver
- verifying that instructions are followed properly
- maintaining accurate records of investigational product dispensing, collection, and administration
- returning all unused medication to Lilly or its designee at the end of the study.

Patients will be instructed to contact the investigator as soon as possible if he or she has a complaint or problem with the investigational product so that the situation can be assessed.

Further instructions and special considerations for the administration of the investigational product are provided in Sections 7.1.1, 7.2.1, and 7.7.2.

Table RHCH.2. Treatment Regimens for Blinded Treatment Dosing Period (Period 2) and Extended Treatment Period (Period 3)

Initial Regimen		Dose Week 0 (Day 1)	Dose Week 4 to Week 12 (Remainder of Period 2)	Dose Week 16	Dose Week 20 to Week 48 (Remainder of Period 3)
	Total injections per patient	**2 injections**	**1 injection Q4W**	**2 injections**	**1 injection Q4W**
Ixekizumab 80 mg Q4W with 160 mg starting dose	Treatment dose	2 ixekizumab 80 mg injections	1 ixekizumab 80 mg injection Q4W	1 ixekizumab 80 mg injection	1 ixekizumab 80 mg injection Q4W
	Injections to maintain blinding	None	None	1 placebo for ixekizumab injection	None
Placebo	Treatment dose	None	None	2 ixekizumab 80 mg injections (starting dose)	1 ixekizumab 80 mg injection Q4W
	Injections to maintain blinding	2 placebo for ixekizumab injections	1 placebo for ixekizumab injection Q4W	None	None

Abbreviations: Q4W = every 4 weeks.

7.1.1. Administration of Investigational Product

Injections will be administered subcutaneously by the patient or clinical site staff or caregiver trained by the clinical site staff.

Training: At Week 0 (baseline, Visit 2) each patient is scheduled to receive 2 injections of blinded investigational product. For training purposes, the first injection will be performed by clinical site staff, and the second injection at that visit will be administered by the patient or caregiver under the supervision of clinical site staff. If additional training is necessary, an injection may be administered by the patient or caregiver under the supervision of clinical site staff at Week 4 (Visit5).

Administration: If the patient is unable to perform the injection, clinical site staff or a caregiver trained by the clinical site staff may administer the investigational product. All subsequent injections of investigational product will be administered either at the clinical site for safety concerns of the patient or outside the clinical site, preferably at patient's home, except for Weeks 0 and 16 when the injections have to be done at the site for post-dose monitoring.

Refer to the appropriate *Manual Syringe Directions for Use* provided by the sponsor for each investigational product. Note that injections are not to be given in the same arm from which patient blood samples, including PK/PD samples, are being drawn at relevant visits.

Study Drug Administration Logs will be dispensed to each patient as needed for recording pertinent data about each injection; details of the use of these logs are provided in Section 7.2.1.

Possible injection sites are identified in the *Manual Syringe Directions for Use*. The injection site is to be rotated to another area for subsequent doses.

Observation: Patients are to remain under observation for at least 1 hour after dosing at Week 0 (Visit 2) and Week 16 (Visit 8) to monitor for safety since some patients will be receiving ixekizumab for the first time at these visits. Therefore, at Week 0 (Visit 2) andWeek 16 (Visit 8), injections of the investigational product will be administered at the clinical site to allow for observation for any AEs and collection of post injection blood pressure (BP) and pulse measurements approximately 1 hour after administration of the investigational product (Section 9.4.2 and Section 2).

7.1.2. Packaging and Labelling

The investigational products will be supplied by the sponsor or its designee in accordance with current Good Manufacturing Practices (cGMP).

Clinical trial materials will be labeled according to the country's regulatory requirements. All investigational products will be stored, inventoried, reconciled, and destroyed according to applicable regulations.

Ixekizumab and placebo to match will be supplied as injectable solutions in 1-mL, single-dose, prefilled, disposable manual syringes with study-specific labels. Each syringe of ixekizumab is designed to deliver ixekizumab 80 mg. The syringes (and contents) containing either

ixekizumab or placebo will be visibly indistinguishable from each other. Syringes will be supplied in cartons, with the appropriate quantity of syringes specific to the planned dispensing schedule of the investigational product.

7.2. Method of Treatment Assignment

Patients who meet all criteria for enrollment will be randomized to double-blind treatment at Week 0 (Visit 2). Assignment to treatment groups will be determined by a computer-generated random sequence using an interactive web-response system (IWRS). The IWRS will be used to assign double-blind investigational product to each patient. Site personnel will confirm that they have located the correct assigned investigational product package by entering a confirmation number found on the package into the IWRS.

To achieve between-group comparability, the randomization will be stratified by baseline CRP (non-elevated or elevated) and TNF inhibitor experienced or naïve. The study will enroll approximately 60% of patients with baseline CRP elevated (>5.00 mg/L) and approximately 40% of patients with non-elevated baseline CRP . At least 61 bDMARD-naïve patients will be enrolled per arm.

Once a specific stratum is fully enrolled, the sponsor may stop further enrollment of patients fitting the criteria of that stratum.

7.2.1. Selection and Timing of Doses

Investigational product is to be administered at approximately the same time each day, as much as possible. For injections not administered on the scheduled day of the week from Weeks 0 to 16, the missed dose is to be administered within 3 days of the scheduled day; after Week 16, the missed dose is to be administered within 5 days of the scheduled day. Dates of subsequent study visits are not to be modified according to this delay.

A paper Study Drug Administration Log will be completed by randomized patients for each injection throughout study participation. The data from the Study Drug Administration Log must be transcribed into the electronic case report form (eCRF) by site personnel.

Patients will be instructed to contact their study site in the event of an injection problem. In addition, site personnel review all Study Drug Administration Logs at each visit to identify any product complaints, and they will complete a Product Complaint Form for each operation failure reported on a Study Drug Administration Log (see Section 9.2.3 for additional instructions regarding complaint handling).

7.3. Blinding

This is a double-blind study.

Initial randomization (study treatment administered between Weeks 0 and 16) will remain blinded to study site personnel and patients until the final clinical trial database lock has occurred.

Randomization will be blinded to sponsor until the clinical trial database through Week 16 has locked

Emergency unblinding for AEs may be performed through the IWRS, which may supplement or take the place of emergency codes generated by a computer drug-labeling system. This option may be used ONLY if the patient's well-being requires knowledge of the patient's treatment assignment. All actions resulting in an unblinding event are recorded and reported by the IWRS.

If an investigator, site personnel performing assessments, or patient is unblinded, the patient is to be discontinued from the study treatment. In cases where there are ethical reasons to have the patient remain on study treatment, the investigator must obtain specific approval from a Lilly clinical research physician or Lilly clinical research scientist for the patient to continue on study treatment.

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a patient's treatment assignment is warranted for medical management of the event. The safety must always be the first consideration in making such a determination. If a patient's treatment assignment is unblinded, Lilly must be notified immediately. If the investigator decides that unblinding is warranted, it is the responsibility of the investigator to promptly document the decision and rationale and notify Lilly as soon as possible.

7.4. Dosage Modification

No investigational product dose modifications are permitted (refer to Section 9.4.10.2.1 for instances where drug may be withheld).

7.5. Preparation/Handling/Storage/Accountability

Investigational products will be supplied by Lilly or its representative, in accordance with cGMP, and will be supplied with lot numbers, expiry dates, and certificates of analysis, as applicable.

The investigational product is to be stored at 2°C to 8°C (36°F to 46°F) in its original carton to protect from light. Investigational product must not be frozen or shaken. Sites will be required to monitor temperature of the on-site storage conditions of the investigational product.

7.6. Treatment Compliance

Patient compliance with study medication will be assessed at each visit. Compliance will be assessed by review of the Study Drug Administration Log, return of empty or unused investigational product packaging, and/or direct questioning. Deviation(s) from the prescribed dosage regimen are to be recorded in the eCRF.

Compliance is defined in Section 10.3.6.4.

7.7. Concomitant Therapy

All concomitant medication taken during the study must be recorded in the eCRF. Patients will maintain their usual medication regimen throughout the study unless specifically excluded in the

protocol. Patients taking permitted medications are to be on stable doses at the baseline visit (Week 0; Visit 2) through Week 16 as specified in inclusion/exclusion criteria (Sections 6.1 and 6.2). Up to Week 16, patients should not start new medications or make any changes to concomitant medications unless changes need to be made for an AE or for safety reasons. Beyond Week 16, some flexibility is allowed in concomitant medication as outlined below.

Additional drugs are to be avoided during the study unless required to treat an AE or for the treatment of an ongoing medical problem. If the need for concomitant medication arises, the investigator is to base decisions on the patient and relevant clinical factors. Any additional medication, whether prescription or over-the-counter, used at baseline (Week 0, Visit 2) and/or during the course of the study must be documented with the start and stop dates in the eCRF. Other medications may be allowed, if approved by the sponsor or its designee.

Only for patients who discontinued study treatment and have entered the Post-Treatment Follow-Up Period (Period 4), AS therapy with another agent previously excluded during the treatment period of the study may be allowed, as determined appropriate by the investigator and approved by Lilly medical.

Patients requiring surgery at any time during the study are to interrupt administration of the investigational product beginning 8 weeks prior to the surgery, or as early as possible within 8 weeks of surgery, and resume administration of the investigational product only after complete wound healing.

Vaccines:

Live vaccines are not allowed during any of the study periods. Use of nonlive seasonal vaccinations and/or emergency vaccination (such as rabies or tetanus vaccinations) is allowed.

NSAIDs and Analgesics:

Blinded Treatment Dosing Period (Period 2):

Nonsteroidal anti-inflammatory drugs, including COX-2 inhibitors, will be allowed up to the maximum recommended doses for pain. Patients must be on a stable dose of NSAIDs/Cox-2 inhibitors for at least 2 weeks prior to baseline randomization. Introduction of a new NSAID or dose adjustment to an existing NSAID is not permitted, unless required for safety reasons.

Short-acting analgesics with no anti-inflammatory action (such as paracetamol) are permitted and may be administered ad hoc as needed and are to be withheld within the 24-hour period prior to any assessment. Aspirin (dose not exceeding 350 mg/day) may be taken to manage cardiovascular risk.

Opiate analgesic use is allowed but not to exceed >30 mg/day of morphine or its equivalent. Patients are to be on stable dose during Period 2. Introduction of a new opiate analgesic or dose adjustment to an existing opiate analgesic is not permitted, unless required for safety reasons or as premedication for MRIs.

Extended Treatment and Post-Treatment Follow-Up Periods (Periods 3 and 4):

After completion of the Week 16 assessments, alterations of NSAIDs, including COX-2 inhibitors (dose change, introduction, or withdrawal) are allowed. Doses are recommended to be stable in the 2 weeks prior to an arthritis assessment.

Short-acting analgesics with no anti-inflammatory action (such as paracetamol) are permitted and may be administered ad hoc as needed but are to be withheld within the 24-hour period prior to any assessment. Aspirin (dose not exceeding 350 mg/day) may be taken to manage cardiovascular risk.

Use of variable doses of opiate analgesics is allowed, but not to exceed an average daily dose of 30 mg morphine or its equivalent.

Conventional DMARDs:

Blinded Treatment Dosing Period (Period 2):

Discontinuation of excluded oral or injectable cDMARDs before study enrollment must occur at least 4 weeks prior to baseline. Methotrexate (oral or parenteral up to 25 mg/week), sulfasalazine (up to 3 g/day), or hydroxychloroquine (up to 400 mg/day) may be allowed IF at stable dose for at least 4 weeks prior to baseline randomization.

During Period 2, alteration of cDMARD dose or route, and/or introduction of a new cDMARD are not permitted, unless required for safety reasons. Conventional DMARDs can only be used as single agents and not in combination with other cDMARDs. If, at any time, the investigator believes that side effects or laboratory abnormalities may be attributable to the cDMARD, the cDMARD dose is to be lowered or the medication stopped.

Extended Treatment and Post-Treatment Follow-Up Periods (Periods 3 and 4):

During Periods 3 and 4, adjustment of allowed cDMARDs (for example, dose change, introduction, withdrawal of cDMARDs, or replacement of a current cDMARD with the introduction of a new cDMARD) is allowed after all assessments at Week 16 are completed. Not more than 1 adjustment of cDMARDs at 1 time within 12 weeks is recommended. Conventional DMARDs can only be used as single agents and not in combination with other cDMARDs. Any changes must be recorded in the eCRF.

For all study periods, the maximum allowed doses are 25 mg/week MTX, 400 mg/day hydroxychloroquine and 3 g/day sulfasalazine. Local standards of care are to be followed for concomitant administration of folic or folinic acid if MTX is taken, and for administration of other cDMARDs.

Corticosteroids:

Blinded Treatment Dosing Period (Period 2):

Oral corticosteroids: If on oral corticosteroids, the dose must not exceed 10 mg/day of prednisone or its equivalent and must be stable for at least 4 weeks prior to baseline randomization. During Period 2, treatment alterations in oral corticosteroid dose are strongly discouraged.

Parenteral corticosteroids (IV, intramuscular, intra-articular): Treatment with any parenteral corticosteroids is not permitted within 6 weeks prior to baseline or during Period 2.

Inhaled and topical steroids: Regular use of inhaled or topical steroids will be permitted during any study period.

Extended Treatment and Post-Treatment Follow-Up Periods (Periods 3 and 4):

Oral corticosteroids: As of Week 16, adjustments of oral corticosteroids are allowed, however the maximum dose is not to exceed 10 mg/day of prednisone or its equivalent at any time during these periods.

Parenteral corticosteroids (IV, intramuscular, intra-articular): As of Week 16, intra-articular injection of corticosteroid may be allowed, as needed. The joint injected must be designated along with the medication in the eCRF.

Inhaled and topical steroids: Regular use of inhaled or topical steroids will be permitted during any study period.

Other Concomitant Medications (Periods 2, 3, and 4):
Patients requiring surgery at any time during the study are to interrupt administration of the investigational product beginning 8 weeks prior to the surgery, or as early as possible within 8 weeks of surgery, and resume administration of the investigational product only after complete wound healing.

Additional drugs are to be avoided during the study unless required to treat an AE or for the treatment of an ongoing medical problem. If the need for concomitant medication arises, the investigator is to base decisions on the patient and on clinical factors. Any additional medication, whether prescription or over-the-counter, used at baseline (Week 0, Visit 2) and/or during the course of the study, must be documented with the start and stop dates in the eCRF.

Additional systemic drugs are to be avoided during the study, unless required to treat an AE. Other medications may be allowed, if approved by the sponsor or its designee.

Only for patients who discontinued study treatment and have entered the Post-Treatment Follow-Up Period, axSpA therapy with another agent previously excluded during the treatment period of the study may be allowed, as determined appropriate by the investigator and approved by Lilly medical.

Any changes in medications not addressed above are to be discussed with the investigator. Patients must be instructed to consult the investigator or other appropriate study personnel at the site before taking any new medications or supplements.

7.7.1. Continued Access

Investigational product will not be made available to patients after conclusion of this study.

7.7.2. Special Treatment Considerations

Patients will be screened for eligibility in the study as described in Sections 6.1 and 6.2 and will be informed of the study-specific restrictions and requirements of the study. Patients who are not willing to comply with the study restrictions and requirements of the study will not be eligible for enrollment.

All biological agents carry the risk of systemic allergic/hypersensitivity reactions (See Section 9.2.2.1).

Sometimes these reactions can be life threatening. Proteins may also cause redness, itching, swelling, or pain locally at the injection site; therefore, all patients should be closely monitored for signs or symptoms that could result from such reactions, educated on the signs or symptoms of these types of reactions, and instructed to contact the study site immediately if any of these symptoms are experienced following an injection. If a patient experiences an acute allergic/hypersensitivity reaction after an injection of investigational product, he or she is to be managed appropriately and given instruction to receive relevant supportive care. Additionally, for an event judged by the investigator to be a potential systemic allergic/hypersensitivity reaction, a blood sample is to be drawn to test for anti-drug antibody (ADA) as soon as possible (see Section 9.4.4).

For patients who experience a potential allergic/hypersensitivity reaction, consideration for any premedication for future injections will be agreed upon between the investigator and sponsor. Examples of potential allergic/hypersensitivity reactions that might merit premedication include mild-to-moderate skin rashes, mild-to-moderate generalized pruritus and/or urticaria, and mild-to-moderate injection site reactions (for example, injection site erythema, injection site pruritus, and so on). Patients who develop clinically significant systemic allergic/ hypersensitivity reactions following administration of investigational product that do not respond to symptomatic medication or result in clinical sequelae (for example, hospitalization) are to be discontinued from study treatment and not receive further doses of investigational product, with or without premedication (see Section 8.1). Medications considered appropriate for premedication include, but are not restricted to, acetaminophen/paracetamol up to 1000 mg and antihistamines (for example, oral diphenhydramine 50 mg) given after all efficacy assessments have been completed for a given visit, and 30 to 60 minutes prior to investigational product SC injections for visits where injections are administered at the clinic. For all other injections, patients may self-premedicate at home prior to administration of investigational product, as directed by the investigator. All such premedications will be recorded as concomitant medications. Corticosteroids are not permitted as agents for premedication.

8. Discontinuation Criteria

8.1. Discontinuation from Study Treatment

The reason for and date of discontinuation from study treatment (investigational product) and reason for and date of discontinuation from study participation will be collected for all randomized patients.

8.1.1. Permanent Discontinuation from Study Treatment

For any patient permanently discontinuing from study treatment, the investigational product will be withheld, and the patient will complete the ETV and the Post-treatment Follow-up Period (Period 4), as shown in the Schedule of Activities (Section 2).

The following criteria must be followed for discontinuation from study treatment.

- **Subject Decision**
  - the patient or the patient's designee, for example, parents or legal guardian requests to discontinue investigational product.
- **Discontinuation due to a hepatic event or liver test abnormality.** Patients who are discontinued from investigational product due to a hepatic event or liver test abnormality should have additional hepatic safety data collected via electronic data entry.

  Discontinuation of the investigational product for abnormal liver tests should be considered by the investigator when a patient meets one of the following conditions, after consultation with the Lilly designated medical monitor:
  - alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >8X upper limit of normal (ULN)
  - ALT or AST >5X ULN for more than 2 weeks
  - ALT or AST >3X ULN and total bilirubin (TBL) level >2xULN or international normalized ratio (INR) >1.5
  - ALT or AST >3X ULN with the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
  - alkaline phosphatase (ALP) >3X ULN
  - ALP >2.5X ULN and TBL >2X ULN
  - ALP >2.5X ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
- Other laboratory tests

- Neutrophil (segmented) counts (see safety monitoring for neutropenia in Section 9.4.10.2):
  - <500 cells/μL (<0.50x10^3/μL or <0.50 GI/L)
  - ≥500 and <1000 cells/μL (≥0.50x10^3/μL and <1.00x10^3/μL or ≥0.50 GI/L and <1.00 GI/L) (based on 2 test results; the second test performed within 1 week from knowledge of the initial result)
  - ≥1000 and <1500 cells/μL (≥1.00x10^3/μL and <1.50x10^3/μL or ≥1.00 GI/L and <1.50 GI/L) (based on 3 test results as specified in Section 9.4.10.2.1)

    - AND - a concurrent infection
- Total WBC count <2000 cells/μL (<2.00x10^3/μL or <2.00 GI/L)
- Lymphocyte count <500 cells/μL (<0.50x10^3/μL or <0.50 GI/L)
- Platelet count <50,000 cells/μL (<50x10^3/μL or <50 GI/L)

- The patient experiences a severe AE, an SAE, or a clinically significant change in a laboratory value that, in the opinion of the investigator, merits the discontinuation of the investigational product and appropriate measures being taken. In this case, Lilly or its designee is to be notified immediately. Refer to Section 9.1.4.
- The investigator, after consultation with the sponsor-designated medical monitor, determines that a clinical significant hypersensitivity reaction has occurred. A clinically significant systemic hypersensitivity reaction is one that occurs after administration of the investigational intervention (for example, drug-related symptomatic bronchospasm, allergy-related edema/angioedema, or hypertension) and requires parenteral medication, does not respond to symptomatic medication, results in clinical sequelae, or in an anaphylactic reaction.
- The patient becomes pregnant.
- The patient develops a malignancy.

  Note: Patients may be allowed to continue if they develop no more than 2 nonmelanoma skin cancers during the study.
- Enrollment in any other clinical trial involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study.

- The patient, at any time during the study, scores a 3 for Item 12 (Thoughts of Death or Suicide) on the QIDS-SR16

  -OR-

  develops active suicidal ideation with some intent to act with or without a specific plan (yes to question 4 or 5 on the "Suicidal Ideation" portion of the Columbia–Suicide Severity Rating Scale [C-SSRS])

  -OR-

  develops suicide-related behaviors as recorded on the C-SSRS.

  It is recommended that the subject be assessed by a psychiatrist or appropriately trained professional to assist in deciding whether the subject is to be discontinued from the study.
- The investigator or attending physician decides that the patient is to be withdrawn from study treatment.
- Lilly or its designee stops the patient's participation in the study or Lilly stops the study for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP).
- The patient becomes HBV DNA positive, at which time the patient is to be referred to a specialist physician. Discussion of the timing of discontinuation from the study and from study treatment is provided in Section 9.4.10.2.2.

Patients discontinuing from the investigational product prematurely for any reason should complete adverse event and other follow-up procedures per Section 2 (Schedule of Activities), Section 9.2 (Adverse Events), and Section 9.4 (Safety) of this protocol.

8.1.2. Discontinuation of Inadvertently Enrolled Patients

If the sponsor or investigator identify a patient who did not meet enrollment criteria and was inadvertently enrolled, then the patient should be discontinued from study treatment unless there are extenuating circumstances that make it medically necessary for the patient to continue on study treatment. If the investigator and the sponsor CRP agree it is medically appropriate to continue, the investigator must obtain documented approval from the sponsor CRP to allow the inadvertently enrolled patient to continue in the study with or without treatment with investigational product. Safety follow up is as outlined in Section 2 (Schedule of Activities), Section 9.2 (Adverse Events), and Section 9.4 (Safety) of the protocol.

8.2. Discontinuation from the Study

Patients will be discontinued in the following circumstances:

- enrollment in any other clinical study involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- participation in the study needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP)
- investigator decision
    - The investigator decides that the patient should be discontinued from the study
    - If the patient, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication, discontinuation from the study occurs prior to introduction of the new agent
- patient decision
    - the patient or the patient's designee, for example, parents or legal guardian requests to be withdrawn from the study

Patients discontinuing from the study prematurely for any reason should complete adverse event and other safety follow-up per Section 2 (Schedule of Activities), Section 9.2 (Adverse Events), and Section 9.4 (Safety) of this protocol.

8.3. Lost to Follow-Up

A patient will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Site personnel are expected to make diligent attempts to contact patients who fail to return for a scheduled visit or were otherwise unable to be followed up by the site.

9. Study Assessments and Procedures

Section 2 lists the Schedule of Activities, with the study procedures and their timing (including tolerance limits for timing).

Appendix 2 lists the laboratory tests that will be performed for this study.

Appendix 4 lists Hepatic Monitoring Tests for Treatment-Emergent Abnormality during the study.

Unless otherwise stated in the subsections below, all samples collected for specified laboratory tests will be destroyed within 60 days of receipt of confirmed test results. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

9.1. Efficacy Assessments

Below are brief descriptions of key aspects of the scales used in the study. Complete assessments are included in site training materials.

The following ASAS domains are used to determine ASAS20, ASAS40, ASAS partial remission, and ASAS 5/6 (Sieper et al. 2009, ASAS Handbook):

1) Patient Global (Section 9.1.2.2)
2) Spinal Pain (Section 9.1.2.3)
3) Function (Section 9.1.2.5)
4) Inflammation (mean of BASDAI questions 5 and 6) (Section 9.1.2.4)
5) CRP (Section 9.1.2.12.1) and
6) Spinal mobility (lateral spinal flexion) (Section 9.1.2.6).

9.1.1. Primary Efficacy Assessments

9.1.1.1. *ASAS40 (in bDMARD-naïve patients)*

The ASAS40 (Anderson et al. 2001; Brandt et al. 2004; Sieper et al. 2009) is derived from patient-reported assessments. An ASAS40 response is defined as a ≥40% improvement and an absolute improvement from baseline of ≥2 units (range 0 to 10) in ≥3 of 4 domains (Patient Global, Spinal Pain, Function, and Inflammation) without any worsening in the remaining domain.

9.1.2. Secondary Efficacy Assessments

9.1.2.1. *ASAS40, ASAS20, ASAS Individual Components, ASAS Partial Remission, and ASAS 5/6*

The ASAS40, ASAS20, ASAS individual components, ASAS partial remission, and ASAS 5/6 responses (Davis et al. 2003; Sieper et al. 2009) are secondary efficacy assessments that are calculated as improvements in respective response rates in multiple disease domains.

Complete definitions of each assessment are provided below.

9.1.2.1.1. ASAS40 (in overall study population)

The ASAS40 (Anderson et al. 2001; Brandt et al. 2004; Sieper et al. 2009) is derived from patient-reported assessments. An ASAS40 response is defined as a ≥40% improvement and an absolute improvement from baseline of ≥2 units (range 0 to 10) in ≥3 of 4 domains (Patient Global, Spinal Pain, Function, and Inflammation) without any worsening in the remaining domain.

9.1.2.1.2. ASAS20

The ASAS20 is derived from patient-reported assessments. An ASAS20 response is defined as a ≥20% improvement and an absolute improvement from baseline of ≥1 units (range 0 to 10) in ≥3 of 4 domains (Patient Global, Spinal Pain, Function, and Inflammation), and no worsening of ≥20% and ≥1 unit (range 0 to 10) in the remaining domain.

9.1.2.1.3. ASAS Partial Remission

The ASAS partial remission is derived from patient-reported assessments. An ASAS partial remission response is defined as a value not above 2 units (range 0 to 10, NRS) in each of the following 4 domains: Patient Global, Spinal Pain, Function, and Inflammation.

9.1.2.1.4. ASAS 5/6

The ASAS 5/6 includes assessment of all 6 individual ASAS domains listed in Section 9.1 and represents improvement of ≥20% in at least 5 domains.

9.1.2.2. *Patient Global (Assessment of Disease Activity)*

From the ASAS Handbook (Sieper et al. 2009), the patient is asked to respond to the following question: "How active was your spondylitis on average during the last week?" The answer is recorded on an NRS and is rated between "0" (not active) and "10" (very active).

9.1.2.3. *Spinal Pain*

From the ASAS Handbook (Sieper et al. 2009), the patient is asked to respond to the following 2 questions (on average during the last week):

1. "How much pain of your spine due to ankylosing spondylitis do you have?"
2. "How much pain of your spine due to ankylosing spondylitis do you have at night?"

The answers are recorded on an NRS and are each rated between "0" (no pain) and "10" (most severe pain). The first question is used to derive responses (that is, ASAS40, ASAS20, and so on).

9.1.2.4. *Bath Ankylosing Spondylitis Disease Activity Index*

The BASDAI is a patient-reported assessment consisting of 6 questions that relate to 5 major symptoms relevant to r-axSpA (Garrett et al. 1994; Sieper et al. 2009): 1) Fatigue, 2) Spinal pain, 3) Peripheral arthritis, 4) Enthesitis, 5) Intensity, and 6) Duration of morning stiffness. Patients need to score each item with a score from 0 to 10 (NRS).

BASDAI50 represents an improvement of ≥50% of the BASDAI score from baseline

9.1.2.5. *Bath Ankylosing Spondylitis Functional Index*

The BASFI is a patient-reported assessment that establishes a patient's functional baseline and subsequent response to treatment (Calin et al. 1995). To complete the BASFI, a patient is asked to rate the difficulty associated with 10 individual basic functional activities. Patients respond to each question using an NRS scale (range 0 to 10) with a higher score indicating worse function.

The patient's final BASFI score is the mean of the 10 item scores completed on an NRS.

9.1.2.6. *Bath Ankylosing Spondylitis Metrology Index—Spinal Mobility*

The BASMI is a combined index comprising the following 5 clinical measurements of spinal mobility in patients with r-axSpA (Jenkinson et al. 1994):

- Lateral spinal flexion
- Tragus-to-wall distance
- Lumbar flexion (modified Schrober)
- Maximal intermalleolar distance
- Cervical rotation.

The BASMI includes these 5 measurements that are each scaled to a score of 0 to 10 depending on the result of the assessment (BASMI linear function). The average score of the 5 assessments gives the BASMI linear result (van der Heijde et al. 2008; Sieper et al. 2009).

The BASMI must be assessed by a rheumatologist or health care provider who meets the qualifications for study assessment.

9.1.2.7. *Chest Expansion*

While patients have their hands resting on or behind the head, the assessor will measure the chest's encircled length by centimeter at the fourth intercostal level anteriorly. The difference between maximal inspiration and expiration in centimeters will be recorded. Two tries will be recorded. The better measurement (larger difference) of 2 tries (in centimeters) will be used for analyses.

The measurement of chest expansion must be assessed by a rheumatologist or health care provider who meets the qualifications for study assessment.

9.1.2.8. *Occiput to Wall Distance*

The patient is to make a maximum effort to touch the head against the wall when standing with heels and back against the wall. Tip of nose and tragus must be at the same horizontal line to avoid neck extension. Then the distance from occiput to the wall is measured. Two tries will be recorded. The better (smaller) measurement of 2 tries (in centimeters) will be used for analyses.

The measurement of occiput to wall distance must be assessed by a rheumatologist or health care provider who meets the qualifications for study assessment.

9.1.2.9. *Ankylosing Spondylitis Disease Activity Score*

The ASDAS is a composite index to assess disease activity in AS (Machado et al. 2011a, 2011b; Zochling 2011; Machado et al. 2018). The parameters used for the ASDAS (with CRP as acute phase reactant) are the following:

1) Total back pain (BASDAI question 2)
2) Patient global (Section 9.1.2.2)
3) Peripheral pain/swelling (BASDAI question 3)
4) Duration of morning stiffness (BASDAI question 6)
5) CRP in mg/L

The $ASDAS_{crp}$ is calculated with the following equation: 0.1216 × total back pain + 0.1106 × patient global + 0.0736 × peripheral pain/swelling + 0.0586 × duration of morning stiffness + 0.5796 × Ln(CRP+1) (Machado et al. 2015). (Note: CRP is in mg/liter, the range of other variables is from 0 to 10; Ln represents the natural logarithm.)

Four disease activity states have been defined by ASAS consensus (Machado et al. 2018):

- ASDAS <1.3 defines inactive disease
- 1.3 ≤ ASDAS <2.1 defines low disease activity
- 2.1≤ ASDAS ≤3.5 defines high disease activity
- ASDAS >3.5 defines very high disease activity.

Clinically important improvement is defined as ≥1.1 units decrease from baseline, and major improvement is defined as ≥2.0 units decrease from baseline or achievement of the lowest possible score (Machado et al. 2011b; Deodhar et al. 2019a).

9.1.2.10. *Maastricht Ankylosing Spondylitis Enthesitis Score*

The MASES is an index used to measure the severity of enthesitis (Heuft-Dorenbosch et al. 2003). The MASES assesses 13 sites for enthesitis using a score of "0" for no activity or "1" for activity. Sites assessed include costochondral 1 (right/left), costochondral 7 (right/left), spinal iliaca anterior superior (right/left), crista iliaca (right/left), spina iliaca posterior (right/left), processus spinosus L5, and Achilles tendon proximal insertion (right/left). The MASES is the sum of all site scores (range 0 to 13); higher scores indicate more severe enthesitis.

The MASES must be assessed by a rheumatologist or health care provider who meets the qualifications for study assessments.

9.1.2.11. *Nonsteroidal Anti-Inflammatory Drug Intake*

Information regarding NSAID intake will be collected in the eCRF; the ASAS-NSAID score will be calculated at baseline and through Week 52 (Dougados et al. 2011).

9.1.2.12. *Laboratory Tests Used for Efficacy Measures and Disease Diagnosis*

9.1.2.12.1. High Sensitivity C-Reactive Protein

High sensitivity CRP will be the measure of acute phase reactant. It will be measured with a high sensitivity assay at the central laboratory to help assess the effect of ixekizumab on disease activity. The results will not be shared with the investigative sites after baseline randomization to maintain the study blind.

9.1.2.13. *Imaging Used for Efficacy Measures and Disease Diagnosis*

9.1.2.13.1. Imaging of Sacroiliac Joints and Spine

For each patient, X-ray and MRI images will be collected according to the Schedule of Activities (Section 2) and Table RHCH.3, and will follow the study-specific recommendations included in site training materials for this study. The SIJ X-ray will be used to confirm patients have radiographic sacroiliitis as defined by the mNY criteria. The spinal MRI, collected at screening, Week 16 and Week 52, will generate objective data on the anti-inflammatory effect of the investigational drug.

The site will send the images (X-ray anterior posterior [AP] Pelvis SIJ and MRI) to the central reader. Images for eligibility and/or for assessment of treatment effect.

Table RHCH.3. Imaging Requirements for Sacroiliac Joints and Spine

Time Point[a]	Type of Image[b]	Purpose	Reading	Requirements
Screening	X-ray AP Pelvis (SIJ)	Eligibility to determine r-axSpA (per mNY criteria)	Centrally read[c]	Send to central reader; results must be received from central reader prior to enrollment
Screening	X-ray of the spine (cervical and lumbar)	Eligibility to determine total ankyloses	Locally read (by investigator)[d]	Not applicable
Screening, Week 16, 52 and ETV	MRI of the spine plus SIJ	Assess efficacy	Centrally read	Send to central reader

Abbreviations: AP = anterior posterior; ETV = early termination visit; mNY = modified New York; MRI = magnetic resonance imaging; r-axSpA = radiographic axial spondyloarthritis; SIJ = sacroiliac joints.

[a] Screening procedures must be conducted within timeframes specified in the Schedule of Activities (Section 2).

b Imaging to be reviewed and approved for quality; imaging that does not pass the quality assessment must be repeated prior to randomization.

c Patient cannot be enrolled until centrally read results are received by site.

d Patient can be enrolled by investigator for this inclusion/exclusion criterion of ankylosis.

9.1.2.13.2. Spondyloarthritis Research Consortium of Canada–MRI Score for Spine

All 23 disco-vertebral units (DVUs) of the spine (from C2 to S1) are scored for bone marrow edema. A single DVU has a scoring range of 0 to 18, bringing the maximum total score to 414, with higher scores reflecting worse disease (Maksymowych et al. 2005a). Scoring will be performed by central readers.

9.1.2.13.3. Spondyloarthritis Research Consortium of Canada–MRI Score for Sacroiliac Joints

Both left and right SIJ are scored for bone marrow edema. Total SIJ SPARCC scores can range from 0 to 72 with higher scores reflecting worse disease (Maksymowych et al. 2005b). Scoring will be performed by central readers.

9.1.2.13.4. Spondyloarthritis Research Consortium of Canada–SIJ Structural Score (SSS)

Structural lesions in MRIs of the SIJ are assessed using the SPARCC SSS method in which the presence or absence of lesions is scored in SIJ quadrants (for fat metaplasia and erosion) or SIJ halves (for backfill and ankylosis). Scoring ranges are fat metaplasia (0 to 40), erosions (0 to 40), backfill (0 to 20), and ankylosis (0 to 20) (Maksymowych et al. 2015). Scoring will be performed by central readers.

9.1.3. Health Outcome Endpoints

9.1.3.1. *European Quality of Life–5 Dimensions 5–Level*

The European Quality of Life–5 Dimensions–5 Level (EQ-5D-5L) is a standardized measure of health status used to provide a simple, generic measure of health for clinical and economic appraisal. The EQ-5D-5L consists of 2 components: a descriptive system of the respondent's health and a rating of his/her current health state using a 0- to 100-mm visual analog scale (VAS). The descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The respondent is asked to indicate his/her health state by ticking (or placing a cross) in the box associated with the most appropriate statement in each of the 5 dimensions. It should be noted that the numerals 1 to 5 have no arithmetic properties and are not to be used as ordinal scores. The VAS records the respondent's self-rated health on a vertical VAS in which the endpoints are labeled "best imaginable health state" and "worst imaginable health state." This information can be used as a quantitative measure of health outcomes. The EQ-5D-5L health states, defined by the EQ-5D-5L descriptive system, may be converted into a single summary index by applying a formula that essentially attaches values (also called weights) to each of the levels in each dimension (EuroQol Group 2011).

9.1.3.2. *Assessment of Spondyloarthritis International Society Health Index*

The ASAS HI is a disease-specific health-index instrument designed to assess the impact of interventions for SpA, including axSpA. This broader concept of health is included in the International Classification of Functioning, Disability, and Health, which has been published by the World Health Organization (WHO). The ASAS has applied this classification as a basis to define a core set of items relevant for patients with AS. The 17-item instrument has scores ranging from 0 (good health) to 17 (poor health) (Kiltz et al. 2013). Each item consists of one question that the patient needs to respond to with either "I agree" (score of 1) or "I do not agree" (score of 0). A score of "1" is given where the item is affirmed, indicating adverse health. All item scores are summed to give a total score or index.

9.1.3.3. *Medical Outcomes Study 36-Item Short-Form Health Survey*

The SF-36 is a 36-item patient-administered measure designed to be a short, multipurpose assessment of health in the areas of physical functioning, role – physical, role – emotional, bodily pain, vitality, social functioning, mental health, and general health. The 2 overarching domains of mental well-being and physical well-being are captured by the mental component summary (MCS) and physical component summary (PCS) scores. The summary scores range

from 0 to 100; higher scores indicate better levels of function and/or better health. Items are answered on Likert scales of varying lengths. The SF-36 version 2 (acute version) will be used, which utilizes a 1-week recall period (Ware 2000).

9.1.3.4. *Functional Assessment of Chronic Illness Therapy Fatigue Scale*

The FACIT Fatigue Scale is a short, 13-item, easy to administer tool that measures an individual's level of fatigue during their usual daily activities over the past 7 days. The level of fatigue is measured on a 5-point Likert-scale (4 = not at all fatigued to 0 = very much fatigued), EXCEPT for items #7 and #8 which are reversely scored. (Webster et al. 2003).

9.1.3.5. *Work Productivity and Activity Impairment Questionnaire–Spondyloarthritis*

The WPAI-SpA consists of 6 questions to determine employment status, hours missed from work because of SpA, hours missed from work for other reasons, hours actually worked, the degree to which SpA affected work productivity while at work, and the degree to which SpA affected activities outside of work. The WPAI-SpA has been validated in the r-axSpA patient population (Reilly et al. 2010). Four scores are derived: percentage of absenteeism, percentage of presenteeism (reduced productivity while at work), an overall work impairment score that combines absenteeism and presenteeism, and percentage of impairment in activities performed outside of work. Greater scores indicate greater impairment (Reilly Associates [WWW]).

9.1.3.6. *Quick Inventory of Depressive Symptomatology–Self-Report (16 Items)*

See Section 9.4.8.

9.1.4. Appropriateness of Assessments

All of the clinical and safety assessments/measures included in the primary and major secondary objectives in this study are standard, widely used, and generally recognized as reliable, accurate,and relevant.

9.2. Adverse Events

An AE is defined as: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Investigators are responsible for monitoring the safety of patients who have entered this study and for alerting Lilly or its designee to any event that seems unusual, even if this event may be considered an unanticipated benefit to the patient.

The investigator is responsible for the appropriate medical care of patients during the study.

Investigators must document their review of each laboratory safety report.

The investigator remains responsible for following, through an appropriate health care option, AEs that are serious or otherwise medically important, considered related to the investigational product or the study, or that caused the patient to discontinue the investigational product before completing the study. The patient should be followed until the event resolves, stabilizes with appropriate diagnostic evaluation, or is reasonably explained. The frequency of follow-up evaluations of the AE is left to the discretion of the investigator.

Lack of drug effect is not an AE in clinical studies, because the purpose of the clinical study is to establish treatment effect.

The investigator will record all relevant AE and SAE information in the case report form (CRF). After the informed consent form (ICF) is signed, study site personnel will record via CRF the occurrence and nature of each patient's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study. In addition, site personnel will record any change in the condition(s) and any new conditions as AEs. Investigators should record their assessment of the potential relatedness of each AE to protocol procedure, investigational product, via CRF.

The investigator will interpret and document whether or not an AE as a reasonably possibility of being related to study treatment, study device, or a study procedure, taking into account the disease, concomitant treatment or pathologies. To assess the relationship of the AEs, the following is defined:

> A "reasonable possibility" means that there is a cause and effect relationship between the investigational product, study device and/or study procedure and the AE.

The investigator answers yes/no when making this assessment.

Planned surgeries and nonsurgical interventions should not be reported as AEs unless the underlying medical condition has worsened during the course of the study.

If a patient's investigational product is discontinued as a result of an AE, study site personnel must report this to Lilly or its designee via electronic data entry, clarifying if possible, the circumstances leading to any dosage modifications, or discontinuations of treatment.

Accurate start and stop dates (and times, where required) are to be reported via electronic data entry for all AEs. Only AEs that are ongoing at the last study visit and/or communication are to be documented as "ongoing".

9.2.1. Serious Adverse Events

An SAE is any AE from this study that results in one of the following outcomes:

- death
- initial or prolonged inpatient hospitalization
- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity

- congenital anomaly/birth defect
- important medical events that may not be immediately life-threatening, or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

All AEs occurring after signing the ICF are recorded in the CRF and assessed for serious criteria. The SAE reporting to sponsor begins after the patient has signed the ICF and has received investigational product. However, if an SAE occurs after signing the ICF, but prior to receiving investigational product, the SAE should be reported to the sponsor as per SAE reporting requirements and timelines (see Section 9.2) if it is considered reasonably possibly related to study procedure.

Study site personnel must alert Lilly or its designee of any SAE within 24 hours of investigator awareness of the event via a sponsor-approved method. If alerts are issued via telephone, they are to be immediately followed with official notification on study-specific SAE forms. This 24-hour notification requirement refers to the initial SAE information and all follow-up SAE information. Patients with a serious hepatic adverse event should have additional data collected using the electronic data entry.

Pregnancy (during maternal or paternal exposure to investigational product) does not meet the definition of an AE. However, to fulfill regulatory requirements any pregnancy should be reported following the SAE process and to collect data on the outcome for both mother and fetus.

Investigators are not obligated to actively seek AEs or SAEs in subjects once they have discontinued and/or completed the study (the patient disposition CRF has been completed). However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably possibly related to the study treatment or study participation, the investigator must promptly notify Lilly.

9.2.1.1. *Suspected Unexpected Serious Adverse Reactions*

Lilly has procedures that will be followed for the identification, recording and expedited reporting of suspected unexpected serious adverse reactions (SUSARs) that are consistent with global regulations and the associated detailed guidances.

9.2.2. Adverse Events of Special Interest

The following adverse events of special interest (AESIs) will be used to determine the safety and tolerability of ixekizumab over the range of doses selected for this clinical study.

The AESIs for ixekizumab are:

- cytopenias (leukopenia, neutropenia, and thrombocytopenia)

- clinically significant hepatic events and/or significant elevations in liver function test changes/enzyme elevations (ALT, AST, bilirubin, and alkaline phosphatase)
- infections
- injection site reactions
- allergic reactions/hypersensitivities
- cerebrocardiovascular events
- malignancies
- IBD
- interstitial lung disease
- depression.

Sites will provide details on some of these AEs as instructed on the CRF. Investigators will also educate patients and/or caregivers about the symptoms of allergic/hypersensitivity reactions and will provide instructions on dealing with these reactions (see also Section 7.7.2). A blood sample is to be collected as soon as possible for any patient who experiences an AE of a potential systemic allergic/hypersensitivity reactions during the study as judged by the investigator.

Data on preferred terms associated with cerebrocardiovascular events (defined as death, cardiac ischemic events including MI and hospitalization for unstable angina, hospitalization for heart failure, serious arrhythmia, resuscitated sudden death, cardiogenic shock, coronary revascularization procedure, stroke/transient ischemic attack, peripheral revascularization procedure, peripheral arterial event, and hospitalization for hypertension) will be collected, and these events and any deaths will be adjudicated by an external clinical events committee (CEC) made up of a chairman, 2 cardiologists, and a neurologist.

Data on suspected IBD, as identified by events possibly indicative of ulcerative colitis and Crohn's disease, will be collected and the events will be adjudicated by an external CEC with expertise in IBD.

The role of external CECs is to adjudicate defined clinical events in a blinded, consistent, and unbiased manner throughout the course of a study. The purpose of the CEC for adjudication of cerebrocardiovascular events and the CEC for adjudication of suspected IBD events is to ensure that all reported events are evaluated uniformly by a single group.

9.2.2.1. *Allergic Reaction and Hypersensitivity Events*

All biologic agents carry the risk of systemic allergic/hypersensitivity reactions. Clinical manifestations of these reactions may include but are not limited to:

- Skin rash
- Pruritus (itching)
- Dyspnea
- Urticarial (hives)
- Angioedema (for example, swelling of the lips and/or tongue)
- Hypotension
- Anaphylactic reaction

Participants with clinical manifestations of systemic allergic/hypersensitivity reactions should be treated per local standard of care. Additional data describing each symptom should be provided to the sponsor in the eCRF.

In case of anaphylaxis or generalized urticaria, additional blood samples should be collected as close as possible to the onset of the event. Follow-up samples should be obtained at the next regularly scheduled visit or 4 weeks after the event, whichever is later. The lab results are provided to the sponsor via the central laboratory or via eCRF.

9.2.3. Complaint Handling

Lilly collects product complaints on investigational products and drug delivery systems used in clinical studies in order to ensure the safety of study participants, monitor quality, and to facilitate process and product improvements.

Patients will be instructed to contact the investigator as soon as possible if he or she has a complaint or problem with the investigational product so that the situation can be assessed.

9.3. Treatment of Overdose

Refer to the IB.

9.4. Safety

9.4.1. Electrocardiograms

For each patient, 12-lead electrocardiograms (ECGs) should be collected locally according to the Schedule of Activities (Section 2). Patients are to be resting for 5 minutes prior to the ECG. It is recommended that patients be in a supine position.

Any clinically significant findings from ECGs that result in a diagnosis and that occur after the patient receives the first dose of the investigational treatment are to be reported to Lilly or its designee as AEs via CRF. Any clinically significant ECG findings prior to receiving drug are to be reported as a preexisting condition.

9.4.2. Vital Signs

For each patient, vital signs measurements are to be conducted according to the Schedule of Activities (Section 2). Vital signs include BP and pulse. Patients are to be resting for a minimum of 5 minutes prior to vital sign collection.

Any clinically significant findings from vital signs measurements that result in a diagnosis and that occur after the patient receives the first dose of study treatment are to be reported to Lilly or its designee as AEs via CRF.

9.4.3. Laboratory Tests

For each patient, laboratory tests (detailed in Appendix 2) shoud be conducted according to the Schedule of Activities (Section 2). For those tests that are tested at the central lab, please reference the central laboratory manual for specific instructions.

With the exception of laboratory test results that may unblind the study, Lilly or its designee will provide the investigator with the results of laboratory tests analyzed by a central vendor, if a central vendor is used for the clinical trial.

Any clinically significant findings from laboratory tests that result in a diagnosis and that occur after the patient receives the first dose of investigational product are to be reported to Lilly or its designee as AEs via CRF.

9.4.4. Immunogenicity Assessments

Where local regulations and ERBs allow, blood samples for immunogenicity testing will be collected to determine antibody production against the investigational product as specified in the Schedule of Activities (Section 2).

Immunogenicity will be assessed using a validated assay designed to detect ADAs in the presence of the investigational product at a laboratory approved by the sponsor. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of the investigational product. Additionally, a blood sample is to be collected, as soon as possible, for any patient who experiences a potential systemic allergic/hypersensitivity reaction during the study as judged by the investigator. These samples will be tested for immunogenicity and PK, while other laboratory tests may be performed as needed to elucidate the cause of the allergic/ hypersensitivity reaction.

Samples will be retained for a maximum of 15 years after the last patient visit for the study, or for a shorter period if regulations and ERBs allow, at a facility selected by the sponsor. The duration allows the sponsor to respond to future regulatory requests related to the investigational product. Any samples remaining after 15 years will be destroyed.

9.4.5. Physical Examination

For each patient, a complete physical examination must be conducted according to the Schedule of Activities (Section 2).

Any clinically significant findings from a complete physical examination that result in a diagnosis and that occur after the patient receives the first dose of study treatment are to be reported to Lilly or its designee as AEs via CRF.

9.4.6. Ocular Examination

At each study visit, investigator or study health care providers will evaluate the patient for any symptoms of anterior uveitis as specified in the Schedule of Activities (Section 2). If the patient develops eye pain or discomfort, eye redness, blurring of vision, or any other symptoms suggestive of anterior uveitis, the patient must be evaluated by an ophthalmologist. The ophthalmologist diagnosis is completed in the CRF.

9.4.7. Chest X-Ray and Tuberculosis Testing

A posterior-anterior view chest X-ray will be obtained, unless the X-ray or results from a chest X-ray obtained within 3 months prior to screening are available. The chest X-ray or results will be reviewed by the investigator or designee to exclude patients with active TB infection.

In addition, patients will be tested at screening and at visits as indicated on the Study Schedule, (Section 2) for evidence of active or latent TB indicated by a positive purified protein derivative (PPD) skin test response (≥5 mm induration, between approximately 2 and 3 days after test application, regardless of BCG vaccination history). If the QuantiFERON®-TB Gold test or T-SPOT® is available and in the judgment of the investigator preferred as an alternative to the PPD skin test for the evaluation of TB infection, either test may be used instead of the PPD test (positive tests excluded) and may be read locally. If the QuantiFERON®-TB Gold or T-SPOT® test is indeterminate, 1 retest is allowed. If the retest is indeterminate, then the patient is excluded from the study.

Patients with documentation of a negative test result within 3 months prior to baseline (Week 0; Visit 2) do not need a TB screen at Visit 1. Documentation of this test result must include a record of the size of the induration response. A PPD test recorded as negative without documenting the size of induration will result in a retest.

If the PPD test is performed and positive (≥5-mm induration) and the patient has no medical history or chest X-ray findings consistent with active TB, a retest can be performed using a quantiFERON®-TB Gold (QTF) or T-SPOT®.TB (T-SPOT) test.

Note: If retest is done with QTF or T-SPOT, this result will be used to determine eligibility in place of the PPD result. Indeterminate results of either test are to be handled as directed above.

However, patients with a PPD skin test ≥5 mm induration or a positive QuantiFERON®-TB Gold or positive T-SPOT® test at screening but no other evidence of active TB may be rescreened 1 time and may be enrolled without repeating a PPD or QuantiFERON® -TB GOLD or T-SPOT® test if the following conditions are met:

- after receiving at least 4 weeks of appropriate latent TB infection (LTBI) therapy,
- with no evidence of hepatotoxicity (ALT/AST must remain ≤2 times ULN) upon retesting of serum ALT/AST prior to randomization. Such patients must complete appropriate LTBI therapy during the course of the study in order to remain eligible, and
- meet all other Inclusion/Exclusion criteria for participation.

If rescreening occurs within 3 months of the screening chest X-ray, there is no necessity for repeat of chest X-ray for considering enrollment. Patients who have a documented history of completing an appropriate TB treatment regimen with no history of re-exposure to TB since their treatment was completed and no evidence of active TB are eligible to participate in the study. Patients who have had household contact with a person with active TB are excluded, unless appropriate and documented prophylaxis for TB was given.

9.4.8. Quick Inventory of Depressive Symptomatology–Self-Report (16 Items)

For each patient, a QIDS-SR16 assessment will be collected according to the Schedule of Activities (Section 2).

Any clinically significant findings from the QIDS-SR16 assessment that result in a diagnosis and that occur after the patient receives the first dose of study treatment are to be reported to Lilly or its designee as AEs via CRF.

The QIDS-SR16 is a self-administered, 16-item instrument intended to assess the existence and severity of symptoms of depression as listed in the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition (APA 1994). A patient is asked to consider each statement as it relates to the way they have felt for the past 7 days. There is a 4-point scale for each item ranging from 0 to 3. The 16 items corresponding to 9 depression domains are summed to give a single score ranging from 0 to 27, with higher scores denoting greater symptom severity. The domains assessed by the instrument are (1) sad mood, (2) concentration, (3) self-criticism, (4) suicidal ideation, (5) interest, (6) energy/fatigue, (7) sleep disturbance (initial, middle, and late insomnia or hypersomnia), (8) decrease/increase in appetite/weight, and (9) psychomotor agitation/retardation. Additional information and the QIDS-SR16 questions may be found at the University of Pittsburgh IDS/QIDS internet page (http://www.ids-qids.org/).

9.4.9. Columbia–Suicide Severity Rating Scale

The C-SSRS (Posner et al. 2007; Columbia University Medical Center [WWW]) is a scale that captures the occurrence, severity, and frequency of suicide-related ideations and behaviors during the assessment period. The C-SSRS must be administered by appropriately trained site personnel. The tool was developed by the National Institute of Mental Health (NIMH) Treatment of Adolescent Suicide Attempters (TASA) trial group for the purpose of being a counterpart to the Columbia Classification Algorithm of Suicide Assessment (C-CASA) categorization of suicidal events. Patients will be assessed according to the Schedule of Activities (Section 2).

The Self-Harm Supplement Form is a one-question form that is completed, at any visit, including baseline visits, that asks for the number of suicidal or nonsuicidal self-injurious behaviors the patient has experienced since the last assessment. For each unique event identified, a questionnaire (Self-Harm Follow-up Form) which collects supplemental information on the self-injurious behavior is to be completed. This information is then documented in the eCRF.

9.4.10. Safety Monitoring

Lilly will periodically review evolving aggregate safety data within the study by appropriate methods.

9.4.10.1. *Hepatic Safety Monitoring*

If a study patient experiences elevated ALT ≥3X ULN, ALP ≥2X ULN, or elevated TBL ≥2X ULN, liver testing (Appendix 4) should be repeated within 3 to 5 days including ALT, AST, ALP, TBL, direct bilirubin, gamma-glutamyl transferase, and creatine kinase to confirm the abnormality and to determine if it is increasing or decreasing. If the abnormality persists or worsens, clinical and laboratory monitoring should be initiated by the investigator and in consultation with the study medical monitor. Monitoring of ALT, AST, TBL, and ALP should continue until levels normalize or return to approximate baseline levels. Details for hepatic monitoring depend upon the severity and persistence of observed laboratory test abnormalities.

Additional safety data should be collected via the CRF/electronic data entry/designated data transmission methods if 1 or more of the following conditions occur:

- elevation of serum ALT to ≥5X ULN on 2 or more consecutive blood tests
- elevated serum TBL to ≥ 2X ULN (except for cases of known Gilbert's syndrome)
- elevation of serum ALP to ≥2X ULN on 2 or more consecutive blood tests
- patient discontinued from treatment due to a hepatic event or abnormality of liver tests
- hepatic event considered to be a SAE

9.4.10.2. *Neutropenia*

9.4.10.2.1. During Treatment (Periods 2 and 3)

During treatment with investigational product, patients with neutrophil counts <1500 cells/μL (<1.50x10^3/μL or <1.50 GI/L) are to be managed for neutropenia as follows:

- <500 cells/μL (<0.50x10^3/μL or <0.50 GI/L), see Discontinuation Criteria (Section 8.1)
- ≥500 cells/μL and <1000 cells/μL (≥0.50x10^3/μL and <1.00x10^3/μL or ≥0.50 GI/L and <1.00 GI/L), see Discontinuation Criteria (Section 8.1)
- ≥1000 cells/μL and <1500 cells/μL (≥1.00x10^3/μL and <1.50x10^3/μL or ≥1.00 GI/L and <1.50 GI/L), and the patient has a concurrent infection that requires systemic anti-infective therapy (for example, antibiotic, antifungal agent, antiviral agent):
    - The dose of investigational product is to be withheld, the patient is to receive appropriate medical care, and a repeat test for neutrophil count is to be performed within 4 weeks from knowledge of the initial report. If the repeat neutrophil count has returned to ≥1500 cells/μL (≥1.50x10^3/μL or ≥1.50x10^3/μL) and the infection has resolved or is resolving, the patient may resume dosing of investigational product and evaluation at scheduled visits. If the neutrophil count remains ≥1000 cells/μL and <1500 cells/μL (≥1.00x10^3/μL and <1.50x10^3/μL or ≥1.00 GI/L and <1.50 GI/L), investigational product is to continue to be withheld and a repeat neutrophil count is to again be performed within another 4 weeks. If, after 2 repeat tests, the neutrophil count still remains ≥1000 cells/μL and

<1500 cells/μL (≥1.00x10^3/μL and <1.50x10^3/μL or ≥1.00 GI/L and <1.50 GI/L), and:

- the infection has not fully resolved, the patient will be discontinued from the study treatment.
- the infection has resolved, the patient may resume dosing and evaluation at scheduled visits. However, if resumption of dosing is not deemed appropriate by the investigator, the patient will be discontinued from the study treatment.

- ≥1000 cells/μL and <1500 cells/μL (≥1.00x10^3/μL and <1.50x10^3/μL or ≥1.00 GI/L and <1.50 GI/L), and the patient has no concurrent infection that requires systemic anti-infective therapy (for example, antibiotic, antifungal agent, antiviral agent):
  - Dosing may continue, and a repeat neutrophil count is to be performed 4 to 8 weeks from knowledge of the initial report. Testing may be at a regularly scheduled visit or at an unscheduled visit, as necessary.
    Repeat testing is to be performed at 4- to 8-week intervals until the neutrophil count has returned to ≥1500 cells/μL (≥1.50x103/μL or ≥1.50 GI/L). If the patient has 3 or more postbaseline neutrophil counts of ≥1000 cells/μL (≥1.00x10^3/μL or ≥1.00 GI/L) and <1500 cells/μL (<1.50x10^3/μL or <1.50 GI/L), no value of <1000 cells/μL (<1.00 x10^3/μL or <1.00 GI/L), and no postbaseline infection requiring systemic anti-infective therapy, the patient may continue or resume further evaluation at scheduled visits, as deemed appropriate by the investigator.

If a patient without initial concurrent infection develops an infection that requires systemic anti-infective therapy, then the patient is to be managed as indicated above for patients with concurrent infection.

9.4.10.2.2. At Early Termination Visit

If at the last scheduled study visit, the patient's neutrophil count is <1500 cells/μL (<1.50x10^3/μL or <1.50 GI/L) and less than the patient's baseline neutrophil count, the following measures are to be taken:

- *Patients with Concurrent Infection:* If there is a concurrent infection that requires systemic anti-infective therapy, the patient is to receive appropriate medical care and a repeat test for neutrophil count is to be performed at least Q4W (or sooner as appropriate) until resolution of infection. Upon resolution of infection, the neutrophil count is to be monitored using the required study visits in Post-Treatment Follow-Up Period (Period 4): Visit 801 (4 weeks post-resolution of infection) and Visit 802 (8 weeks after Visit 801 unless otherwise specified). Additional monitoring may be required if it is deemed necessary by the investigator.
- *Patients without Concurrent Infection:* If there is no concurrent infection that requires systemic anti-infective therapy, the neutrophil count is to be monitored using the required study visits in the Post-Treatment Follow-Up Period (Period 4): Visit 801 (4

weeks post-ETV or last regularly scheduled visit) and Visit 802. Additional monitoring may be required if it is deemed necessary by the investigator.

9.4.10.2.3. Post-Treatment Follow-Up Period

At Visit 801 and V802, the following monitoring applies:

- As long as a patient's neutrophil count is <1000 cells/μL (<1.00x10^3/μL or <1.00 GI/L) at any follow-up visit, the patient is to return for visits at least Q4W (may require unscheduled visits).
- As long as a patient's neutrophil count is ≥1000 cells/μL and <1500 cells/μL (≥1.00x10^3/μL and <1.50x10^3/μL or ≥1.00 GI/L and <1.50 GI/L) at any follow-up visit, the patient is to return for additional visit(s) at least every 4 to 8 weeks (may require unscheduled visits).

If, at Visit 802, the patient's neutrophil count remains <1500 cells/μL (<1.50x10^3/μL or <1.50 GI/L) and less than the patient's baseline neutrophil count, or if the investigator deems additional follow-up may be necessary, the investigator will determine the appropriate management of the patient and the appropriate timing of additional contact(s).

9.4.10.3. *Hepatitis B Monitoring*

Patients that are HBcAb+ at screening, regardless of other hepatitis B testing results, will have a serum HBV DNA specimen obtained to be analyzed by the central laboratory. Such patients that are determined to be HBV DNA negative (undetectable) may be enrolled into the study with required HBV DNA monitoring every 3 to 4 months during treatment and 12 weeks after the last dose of ixekizumab. Patients that are found to be HBV DNA positive (detectable) at screening will be excluded from the trial.

If the result of any subsequent HBV DNA testing is positive, the patient is to be discontinued from the study treatment, is to continue safety follow up, and is to receive appropriate follow-up medical care, including consideration for antiviral therapy. A specialist physician in the care of patients with hepatitis (for example, infectious disease or hepatologist subspecialists) is to be consulted and potentially start antiviral therapy prior to discontinuation of any immunosuppressant or immunomodulatory therapy (including investigational drug). Timing of discontinuation from the study and of any immunosuppressant/immunomodulatory therapy (including investigational product) needs to be based on the recommendations of the consulting specialist physician in conjunction with the investigator and medical guidelines/standard of care.

9.4.10.4. *Hypertension*

Patients who experience changes in BP (systolic BP at ≥160 mm Hg plus ≥20 mm Hg increase from baseline [Week 0, Visit 2]; and/or diastolic BP at ≥100 mm Hg plus ≥10 mm Hg increase from baseline) on 2 consecutive visits are to receive intervention for the management of hypertension. Intervention could include the maximal intervention of withholding the dose of investigational product and/or the introduction of anti-hypertensive agent(s) as medically appropriate.

For other AESIs or abnormal lab results, please refer to the appropriate protocol section that addresses these topics. To ensure patient safety and comply with regulatory guidance, the investigator is to consult with the Lilly clinical research physician/clinical research scientist regarding collection of specific recommended clinical information and follow-up laboratory tests. See Appendix 4.

9.5. Pharmacokinetics

At the visits and times specified in the Schedule of Activities (Section 2), venous blood samples of approximately 4 mL each will be collected to determine the serum concentrations of ixekizumab. These blood samples for PK analysis are matched to the timing of samples for the assessment of immunogenicity. It is expected that these PK samples will allow sufficient description of ixekizumab PK profiles at steady state throughout the study. Instructions for the collection and handling of blood samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sampling will be recorded.

Samples collected for PK analysis will be tested at a laboratory approved by Lilly or its designee. Concentrations of immunoreactive ixekizumab in human serum will be determined by a validated method.

Bioanalytical samples collected to measure investigational product concentration will be retained for a maximum of 1 year following last patient visit for the study.

9.6. Pharmacodynamics

Not applicable

9.7. Genetics

Not applicable.

9.8. Health Economics

Refer to 9.1.3.

10. Statistical Considerations

10.1. Sample Size Determination

Approximately 140 patients will be randomized at a 1:1 ratio in the Blinded Treatment Dosing Period (Period 2) to ixekizumab 80 mg Q4W with a starting dose 160 mg and placebo.

For 90% power to test the superiority of ixekizumab Q4W to placebo for ASAS40 at Week 16 in bDMARD-naïve patients, at least 61 bDMARD-naïve patients per treatment group would be needed. The following assumptions were used for the power calculations for ASAS40 response rates: 44% for ixekizumab 80 mg Q4W treatment group and 16% for the placebo group in bDMARD naïve patients.

For the key secondary efficacy endpoint ASAS40 response at Week 16 compared to placebo group in overall study population, the power would be >90%. The assumptions are 42% response rate for ixekizumab 80 mg Q4W treatment group and 15% for the placebo group in overall study population.

These assumptions are based on the review of historical clinical studies in r-axSpA (etanercept, adalimumab, infliximab, certolizumab, and golimumab [Davis et al. 2003; van der Heijde et al. 2005, 2006; Inman et al. 2008, Landewé et al. 2014]) and recent secukinumab trials including both TNF inhibitor experienced patients and naïve patients (Baeten et al. 2014b; Sieper et al. 2014).

A 2-sided Fisher's exact test at the 0.05 level is assumed. Sample size and power estimates were obtained from nQuery® Advisor 7.0.

10.2. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Intent-to-Treat Population (ITT)	Unless otherwise specified, efficacy and health outcomes analyses for Period 2 will be conducted on the ITT population, defined as all randomized patients, even if the patient does not take the assigned treatment, does not receive the correct treatment, or otherwise does not follow the protocol. Patients will be analyzed according to the treatment to which they were assigned.
Per-Protocol Set (PPS)	In addition, the primary efficacy analysis will be repeated using the PPS, which is defined as all randomized patients who are compliant with therapy, who do not have a subset of important protocol deviations that impact the primary efficacy endpoint, and whose investigator site does not have significant GCP issues that require a report to the regulatory agencies prior to Week 16 (Visit 8). Compliance with therapy is defined to be missing no more than 20% of expected doses, not missing 2 consecutive doses (all injections at a visit are counted as 1 dose), and not have any occurrence of over-dosing (that is, took more injections at the same time point than specified in the protocol)

	during Period 2. Important protocol deviations will be described in the SAP. Patients will be analyzed according to the treatment to which they were assigned.
Safety Population	Safety analyses for Period 2 will be conducted on the Safety Population, defined as all randomized patients who received at least 1 dose of study treatment. Patients will be analyzed according to the treatment to which they were assigned in that period.
Extended Treatment Period Population	Efficacy, health outcomes, and safety analyses for Period 3 will be conducted on the Extended Treatment Period Population, defined as all patients who received at least 1 dose of ixekizumab treatment during Period 3.
Follow-Up Population	Safety analyses for Period 4 will be conducted on the Follow-Up Population, defined as all randomized patients who received at least 1 dose of study treatment and have entered Period 4. Patients will be analyzed according to the treatment they received before entering Period 4.

Abbreviations: GCP = good clinical practice; ITT = Intent-to-Treat Population; PPS = Per-Protocol Set; SAP = statistical analysis plan.

10.3. Statistical Analyses

Statistical analysis of this study will be the responsibility of Lilly.

Continuous data will be summarized in terms of the mean, standard deviation, minimum, maximum, median, and number of observations. Categorical data will be summarized as frequency counts and percentages.

Any change to the data analysis methods described in the protocol will require an amendment ONLY if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the clinical study report (CSR). Additional exploratory analyses of the data will be conducted as deemed appropriate.

Complete details of the planned analyses will be documented in the SAP.

10.3.1. General Considerations for Analyses during the Blinded Treatment Dosing Period (Period 2)

Comparison between ixekizumab 80 mg Q4W and placebo will be performed for all analyses in Period 2.

Period 2 starts at the first injection of study treatment at Week 0 (Visit 2) and ends prior to the first injection of study treatment at Week 16 (Visit 8) or the ETV (between Weeks 0 and 16).

Baseline will be defined as the last available value before the first injection for efficacy, health outcomes, and safety analyses. In most cases, this will be the measure recorded at Week 0 (Visit 2). For efficacy measures, if the patient does not take any injection, the last available value on or prior to randomization date will be used. Change from baseline will be calculated as the visit value of interest minus the baseline value. For safety analyses using a baseline period, the baseline period is defined as the time from Visit 1 to the date/time of the first injection.

The randomization to treatment groups is stratified by baseline CRP status (non-elevated or elevated) and TNF inhibitor experienced or naïve as described in Section 7.2. Unless otherwise specified, the statistical analysis models will adjust for baseline CRP status, and prior TNF inhibitor experienced or naïve (if applicable).

The primary analysis method for treatment comparisons of categorical efficacy and health outcomes variables at specific time points will be made using a logistic regression analysis with treatment, baseline CRP status, and TNF inhibitor experienced or naïve (if applicable) in the model. The proportions, odds ratio and 95% confidence intervals (CIs) will be reported; treatment difference and 95% CIs will also be reported. Secondary analysis will be conducted using a Fisher's exact test.

The primary analyses for continuous efficacy and health outcomes variables will be made using MMRM. A secondary analysis for continuous efficacy and health outcomes variables may also be made using analysis of covariance (ANCOVA).

When the MMRM is used, the model will include treatment, baseline CRP status, TNF inhibitor experienced or naïve, baseline value, baseline value-by-visit, visit, and treatment-by-visit interaction as fixed factors. The covariance structure to model the within-patient errors will be unstructured. If the unstructured covariance matrix results in a lack of convergence, the heterogeneous Toeplitz covariance structure, followed by the heterogeneous autoregressive covariance structure, followed by the compound symmetry, will be used. This order is specified according to a decreasing number of covariance parameters in the structure. The Kenward-Roger method will be used to estimate the denominator degrees of freedom. Type III tests for the least-squares (LS) means will be used for the statistical comparison; the 95% CI will also be reported. Treatment group comparisons with placebo at Week 16 (Visit 8) and all other visits will be tested.

When the ANCOVA is used, the model will include treatment, baseline CRP status, TNF inhibitor experienced or naïve, and baseline value. Type III sums of squares for the LS means will be used for the statistical comparison; the 95% CI will also be reported.

For variables that are not collected at each postbaseline visit, data may exist at visits where the variable was not scheduled to be collected, due to early discontinuation visits. In these situations, data from the early discontinuation visit that do not correspond to the planned collection schedule will be excluded from the MMRM analyses. However, the data will still be used in other analyses, including shift analyses, modified baseline observation carried forward (mBOCF) endpoint analyses and other categorical analyses.

Fisher's exact test will be used for all AE, baseline, discontinuation, and other categorical safety data. Continuous vital sign and laboratory values will be analyzed by an ANCOVA with treatment and baseline value in the model.

10.3.2. General Considerations for Analyses during the Extended Treatment Period (Period 3)

Unless otherwise specified, Period 3 starts at the first injection of study treatment at Week 16 (Visit 8) and ends on the date of Week 52 (Visit 17) or the ETV (between Weeks 16 and 52).

For the efficacy and health outcomes analyses, baseline is defined as the last available value before the first injection in Period 2 and, in most cases, this will be the value recorded at Week 0 (Visit 2).

Unless otherwise specified, for the safety analyses during Period 3, baseline is defined as the last available value before first injection of ixekizumab in Period 3. In most cases, this will be the measure recorded at Week 16 (Visit 8).

All efficacy and safety data collected will be summarized using descriptive statistics.

10.3.3. General Considerations for Analyses during the Post-Treatment Follow-Up Period (Period 4)

For the safety analyses during Period 4, baseline is defined as the last nonmissing assessment on or prior to entering Period 4, that is, on or prior to Week 52 (Visit 17), or ETV.

Safety data collected will be summarized using descriptive statistics.

10.3.4. Missing Data Imputation

In accordance with precedent set with other Phase 3 axSpA trials (van der Heijde et al. 2006; Inman et al. 2008), the following methods for imputation of missing data will be used.

10.3.4.1. *Nonresponder Imputation*

Analysis of categorical efficacy and health outcomes variables will be assessed using a nonresponder imputation (NRI) method. Patients will be considered nonresponders for the NRI analysis if they do not meet the clinical response criteria or have missing clinical response data at the primary analysis time point. All nonresponders at Week 16 (Visit 8), as well as all patients who discontinue study treatment at any time prior to Week 16 for any reason, will be defined as nonresponders for the NRI analysis at Week 16. Randomized patients without at least 1 postbaseline observation will also be defined as nonresponders for the NRI analysis.

The NRI may be applied at any time point specified for analysis.

10.3.4.2. *Modified Baseline Observation Carried Forward*

An mBOCF analysis will be performed on efficacy and health outcomes variables in the major and other secondary objectives. For patients discontinuing study drug due to an AE, the baseline observation will be carried forward to the corresponding time point for evaluation. For patients discontinuing study drug for any other reason, the last nonmissing observation before discontinuation will be carried forward to the corresponding time point for evaluation. Randomized patients without at least 1 postbaseline observation will not be included for evaluation with the exception of patients discontinuing study treatment because of an AE.

10.3.5. Adjustment for Multiple Comparisons

A multiple testing strategy for the primary and major secondary objectives will be implemented to control the overall family-wise type I error rate at a 2-sided α level of 0.05. A graphical multiple testing procedure (Bretz et al. 2011) will be used. The graphical approach is a closed testing procedure; hence, it strongly controls the family-wise error rate (Alosh et al. 2014). The following is a list of primary and major secondary outcomes to be tested for ixekizumab 80 mg Q4W at Week 16:

- Primary: proportion of patients achieving an ASAS40 response [ASAS40 naïve] in bDMARD-naïve patients
- Secondary 1: proportion of patients achieving an ASAS40 response [ASAS40 overall] in overall study population
- Secondary 2: proportion of patients achieving an ASAS20 response [ASAS20] in overall study population
- Secondary 3: change from baseline in ASDAS score [ASDAS CFB] in overall study population
- Secondary 4: change from baseline in BASDAI [BASDAI CFB] in overall study population
- Secondary 5: change from baseline in BASFI [BASFI CFB] in overall study population
- Secondary 6: proportion of patients achieving ASDAS < 2.1 [ASDAS < 2.1] in overall study population
- Secondary 7: change from baseline in MRI of the spine [MRI spine SPARCC score CFB] in overall study population
- Secondary 8: change from baseline in SF-36 PCS score [SF-36 PCS CFB] in overall study population

Details of the specific graphical testing scheme (including testing order, interrelationships, type I error allocation for the major secondary endpoints, and the associated propagation of α) to be implemented will be prespecified in the SAP prior to first unblinding.

There will be no adjustment for multiple comparisons for any other analyses.

10.3.6. Treatment Group Comparability

10.3.6.1. *Patient Disposition*

All patients who prematurely discontinue from the study treatment and/or from the study will be identified, and the extent of their participation in the study will be reported.

Patient disposition will be summarized for each treatment period with reasons for discontinuation. The reasons for discontinuation during Period 2 will be compared between treatment groups using Fisher's exact test.

10.3.6.2. *Patient Characteristics*

Patient characteristics and baseline clinical measures will be summarized for each treatment period. Baseline characteristics will include sex, age, age category, weight, body mass index

(BMI), race, baseline disease activity (BASDAI), duration of disease, HLA-B27 positivity, baseline CRP (% of non-elevated or elevated), baseline MRI status, number of prior TNF inhibitor experienced or naïve, and history of extra-axial disease manifestations. Baseline clinical measurements may include ASDAS, CRP, BASFI, BASMI, chest expansion, FACIT, Patient Global NRS, total back pain, spinal pain at night due to AS, spinal pain due to AS, inflammation (mean of questions 5 and 6 of BASDAI), MASES.

Treatment group comparisons in Period 2 will be conducted using Fisher's exact test for categorical data and an analysis of variance (ANOVA) with treatment as a factor for continuous data.

10.3.6.3. *Concomitant Therapy*

Previous and concomitant medications will be summarized for patients who enter each treatment period and will be presented by WHO Anatomic Therapeutic Class Level 4 and WHO preferred term. Concomitant DMARDs, concomitant oral corticosteroids, and concomitant NSAIDs will also be summarized. Treatment group comparisons in Period 2 will be conducted using Fisher's exact test.

10.3.6.4. *Treatment Compliance*

Treatment compliance with investigational product will be summarized for patients who enter each treatment period. A patient will be considered overall compliant for each study period if he/she is missing no more than 20% of the expected doses, does not miss 2 consecutive doses and does not over-dose (that is, take more injections at the same time point than specified in the protocol).

Proportions of patients compliant by visit and overall will be compared between treatment groups during Period 2 using Fisher's exact test.

10.3.7. Efficacy Analyses

10.3.7.1. *Primary Analyses*

The primary analysis, the proportion of patients with ASAS40 at Week 16 compared with placebo, will be based on the ITT Population in bDMARD-naïve patients. In addition, an analysis of the PPS Population will be used to support the primary efficacy analysis.

Treatment comparisons between the ixekizumab treatment group and placebo in the proportion of patients achieving an ASAS40 response at Week 16 (Visit 8) will be analyzed using the logistic regression model defined in Section 10.3.1. Missing data will be imputed using the NRI method described in Section 10.3.4.

Secondary analyses for ASAS40 at Week 16 will be conducted using Fisher's exact test as described in Section 10.3.1.

10.3.7.2. *Secondary Analyses*

10.3.7.3. *Major Secondary Analyses*

The major secondary analyses at Week 16 will be based on the ITT population for Period 2. The major secondary comparisons will be based on the multiple testing procedure detailed in Section 10.3.5. Treatment comparisons in the proportion of patients achieving a categorical response at Week 16 (Visit 8) will be analyzed using the logistic regression model defined in Section 10.3.1. For categorical responses, missing data will be imputed using the NRI method described in Section 10.3.4. Treatment comparisons in the continuous measures will be analyzed using the MMRM model defined in Section 10.3.1.

Table RHCH.4 summarizes the primary and major secondary outcomes and analysis methods. All analyses listed will be performed based on the ITT Population unless otherwise specified.

Table RHCH.4. Primary and Major Secondary Outcome Analyses

Outcome Measure	Primary Analysis Method	Secondary Analysis Method
ASAS40 (primary efficacy outcome) in bDMARD-naïve patients	Logistic regression analysis with NRI	Fisher's exact test with NRI Logistic regression analysis with NRI on PPS
ASAS40 (major secondary outcome) in overall study population	Logistic regression analysis with NRI	Fisher's exact test with NRI Logistic regression analysis with NRI on PPS
ASAS20 (major secondary outcome)	Logistic regression analysis with NRI	Fisher's exact test with NRI
Change from baseline in ASDAS (major secondary outcome)	MMRM	ANCOVA with mBOCF
Change from baseline in BASDAI (major secondary outcome)	MMRM	ANCOVA with mBOCF
Change from baseline in BASFI (major secondary outcome)	MMRM	ANCOVA with mBOCF
ASDAS < 2.1 (major secondary outcome)	Logistic regression analysis with NRI	Fisher's exact test with NRI
Change from baseline in MRI of spine [SPARCC score] (major secondary outcome)	ANCOVA with observed case analysis[a]	Secondary analysis maybe specified in SAP
Change from baseline in SF-36 PCS (major secondary outcome)	MMRM	ANCOVA with mBOCF

Abbreviations: ANCOVA = analysis of covariance; ASAS = Assessment of Spondyloarthritis International Society; ASDAS = Ankylosing Spondylitis Disease Activity Score; BASDAI50 = Bath Ankylosing Spondylitis Disease Activity Index 50; BASFI = Bath Ankylosing Spondylitis Functional Index; mBOCF = modified baseline observation carried forward; MMRM = mixed-effects model of repeated measures; MRI = magnetic resonance imaging; NRI = nonresponder imputation; PPS = per-protocol set; SAP = statistical analysis plan; SF-36 PCS = Short Form-36 physical component scores; SPARCC = Spondyloarthritis Research Consortium of Canada.

[a] Only patients with both baseline and Week 16 MRI scores will be included in the observed case analysis.

10.3.7.4. *Other Secondary Efficacy Analyses*

There will be no adjustment for multiple comparisons. Analyses will be conducted for the other secondary efficacy objectives defined in Section 4. Specific details of analyses will be specified in the SAP.

Period 2 (Blinded Treatment Dosing Period)

Unless otherwise specified, the other secondary analyses during Period 2 will be based on the ITT Population.

Treatment comparisons in the proportion of patients achieving a categorical response at specified time points will be analyzed using the logistic regression model defined in Section10.3.1. Missing data will be imputed using the NRI method described in Section 10.3.4.

For all continuous efficacy variables that are collected at repeated visits, treatment group comparisons will be analyzed using the MMRM model defined in Section 10.3.1. No imputation

methods are applied to MMRM analysis. Additional analyses will be conducted using the ANCOVA model defined in Section 10.3.1; missing data will be imputed by the mBOCF method as described in Section 10.3.4. For continuous efficacy variables that are collected only once within Period 2, analyses will be made using the ANCOVA model with the mBOCF method.

10.3.7.4.1. Period 3 (Extended Treatment Period)

Data collected in this study period will be summarized for the Extended Treatment Period Population.

10.3.7.5. *Tertiary/Exploratory Analyses*

Details about exploratory analyses will be included in the SAP.

10.3.8. Safety Analyses

Safety will be assessed by summarizing and analyzing AEs including adjudicated cerebrocardiovascular events, laboratory analytes including neutrophil counts, QIDS-SR16, C-SSRS, and vital signs. The duration of treatment exposure will also be summarized

For Period 2 (Blinded Treatment Dosing Period), safety data will be summarized for the Safety Population. Treatment group comparisons will be performed on categorical safety data using Fisher's exact test as described in Section 10.3.1; continuous safety data will be analyzed by an ANCOVA model.

For Period 3 (Extended Treatment Period), the safety data will be summarized.

For Period 4 (Post-Treatment Follow-Up Period), safety data will be summarized according to the treatment patients were on prior to entering Period 4.

The categorical safety measures will be summarized with incidence rates. The mean change of the continuous safety measures will be summarized by visits.

Further details will be described in the SAP.

10.3.8.1. *Adverse Events*

Adverse events are classified based upon the Medical Dictionary for Regulatory Activities (MedDRA). A treatment-emergent adverse event (TEAE) is defined as an event that first occurred or worsened in severity after baseline and on or prior to the date of the last visit within the treatment period. Both the date/time of the event onset and the date/time of the first study drug injection are considered when determining TEAEs. Treatment-emergent adverse events will be assigned to the treatment period in which they first occurred or worsened. A follow-up emergent adverse event (FEAE) is defined as an event that first occurred or worsened in severity after the date of Week 52 (Visit 17) or the ETV. For events that are gender specific, the denominator and computation of the percentage will include only patients from the given gender.

An overall summary of AEs will be provided for each of the treatment periods, including the number and percentage of patients who experienced TEAEs, TEAEs by maximum severity, deaths, SAEs, TEAEs related to study drug, discontinuations from the treatment due to an AE, and treatment-emergent AESIs. Treatment-emergent adverse events (all, by maximum severity,

and TEAEs possibly related to study drug by the investigator), SAEs including deaths, and AEs that lead to treatment discontinuation will be summarized and analyzed by MedDRA system organ class (SOC) and preferred term.

In addition to general safety parameters, safety information on specific topics of AESIs will also be presented. Potential AESIs will be identified by a standardized MedDRA query (SMQ) or a Lilly defined MedDRA preferred term listing.

Follow-up emergent adverse events, SAEs including deaths, and AEs that lead to study discontinuation will be summarized for Period 4.

10.3.8.2. *Clinical Laboratory Tests*

Laboratory assessments will be presented as mean changes from baseline, and as incidence of treatment-emergent abnormal, high, or low laboratory values (see below). Shift tables will be presented for selected parameters.

- For categorical lab tests:
  - Treatment-emergent **abnormal** value = a change from normal at all baseline visits to abnormal at any time postbaseline.
- For continuous lab tests:
  - Treatment-emergent **high** value = a change from a value less than or equal to the high limit at all baseline visits to a value greater than the high limit at any time postbaseline.
  - Treatment-emergent **low** value = a change from a value greater than or equal to the low limit at all baseline visits to a value less than the low limit at any time postbaseline.

10.3.8.3. *Vital Signs, Physical Findings, and Other Safety Evaluations*

Vital signs will be presented as mean changes from baseline and as incidence of treatment-emergent high or low values (see below) and will be summarized both pre- and postdose at Week 0 (Visit 2) and Week 16 (Visit 8) as applicable.

- For treatment-emergent high and low:
  - A treatment-emergent high result is defined as a change from a value less than or equal to the high limit at baseline to a value greater than the high limit at any time that meets the specified change criteria during the treatment period.
  - A treatment-emergent low result is defined as a change from a value greater than or equal to the low limit at baseline to a value less than the low limit at any time that meets the specified change criteria during the treatment period.

The maximum postbaseline QIDS-SR16 total score will be summarized by treatment group, and a shift table will be produced for the change from baseline in QIDS-SR16 total score category.

Suicide-related thoughts and behaviors and self-injurious behavior with no suicidal intent, based on the C-SSRS, will be listed by patient.

10.3.9. Pharmacokinetic/Pharmacodynamic Analyses

Observed ixekizumab serum concentrations will be summarized by treatment regimen, visits and corresponding time when sampling occurred.

As appropriate, the PK and the exposure-response relationship between ixekizumab exposure and clinically important efficacy measures (for example, ASAS40 or ASAS20) may be explored using graphical methods and/or a modeling approach. Pharmacokinetic and/or exposure-response data from this study may be combined with existing PK and/or exposure-response data from other studies, if considered appropriate.

In addition, the potential impact of immunogenicity on ixekizumab exposure may be evaluated by graphical assessments, as appropriate, to compare drug exposure between ADA negative and ADA positive patients at corresponding visits, or before and after ADA development for patients who develop ADA. Both treatment-emergent only and all ADA positive/negative patients may be explored. A similar approach may be taken if patients become NAb positive.

10.3.10. Other Analyses

10.3.10.1. Health Economics

There will be no adjustment for multiple comparisons. Analyses will be conducted for the other secondary health outcomes objectives as defined in Section 4.

Period 2 (Blinded Treatment Dosing Period):

Unless otherwise specified, the other secondary analyses during Period 2 will be based on the ITT Population.

Treatment comparisons in the proportion of patients achieving a categorical response at specified time points will be analyzed using the logistic regression model defined in Section 10.3.1. Missing data will be imputed using the NRI method described in Section 10.3.4.

For all continuous health outcomes variables that are collected at repeated visits, treatment group comparisons will be analyzed using the MMRM model defined in Section 10.3.1 if appropriate. No imputation methods are applied to MMRM analysis. Additional analyses may be conducted using the ANCOVA model defined in Section 10.3.1; missing data will be imputed by the mBOCF method as described in Section 10.3.4. For continuous health outcomes variables that are collected only once within the Period 2, analyses will be made using the ANCOVA model with the mBOCF method.

Period 3 (Extended Treatment Period):

Data collected in Period 3 will be summarized for the Extended Treatment Period Population.

Additional analyses of health outcomes measures will be specified in the SAP.

10.3.10.2. Subgroup Analyses

Subgroup analyses will be conducted for ASAS40 and selective major secondary outcomes (defined in the SAP) at Week 16 (Visit 8) using the ITT Population.

Subgroup analyses may be conducted based on gender, age category, baseline disease severity, baseline CRP status, baseline MRI status, prior TNF inhibitor experience, and presence of HLA-B27.

For ASAS40, a logistic regression model with treatment, subgroup, and the interaction of subgroup-by-treatment included as factors will be used. The subgroup-by-treatment interaction will be tested at the significance level of 0.10. Treatment group differences will be evaluated within each category of the subgroup using Fisher's exact test, regardless of whether the interaction is statistically significant. Missing data will be imputed using NRI as described in Section 10.3.4. If any group within the subgroup is <10% of the total population, only summaries of the efficacy data will be provided (that is, no inferential testing).

For continuous efficacy outcome (for example, mean change from baseline in ASDAS), an ANCOVA model with treatment, baseline value, subgroup, and the interaction of subgroup-by-treatment will be used. The subgroup-by-treatment interaction will be tested at the significance level of 0.10. Treatment group differences will be evaluated within each category of the subgroup using an ANCOVA model with treatment and baseline value as a covariate, regardless of whether the interaction is statistically significant. Missing data will be imputed using the mBOCF method as described in Section 10.3.4.

Detailed description of the subgroup variables will be provided in the SAP. Additional subgroup analyses on efficacy or subgroup analyses on safety may be performed as deemed appropriate and necessary.

10.3.11. Immunogenicity

The analyses of ADA effects will be conducted on all evaluable patients within the defined safety population. Evaluable patients will be defined as either a) patients with an evaluable baseline sample and at least 1 evaluable postbaseline sample (that is, sample after administration of study drug); or b) patients with no evaluable baseline sample whose evaluable postbaseline samples were all ADA negative.

A TE-ADA positive patient will be defined as any occurrence of a ≥4-fold or 2 dilution increase in immunogenicity titer over the baseline titer. This is equivalent to an increase in titer to ≥1:10, in the case of a negative result at baseline. The frequency and percentage (incidence) of patients with positive, negative, or inconclusive ADA at baseline and postbaseline (and NAb at baseline and postbaseline) will be summarized by treatment group. Patients who are TE-ADA positive, TE-ADA persistent positive, and TE-ADA transient positive will also be summarized.

The potential impact of immunogenicity on ixekizumab exposure and/or efficacy responses will be evaluated, as appropriate.

Assessment of immunogenicity with respect to safety will include comparison of patients who experience TEAEs of systemic allergy/hypersensitivity and of injection-site reactions and who also develop treatment-emergent anti-ixekizumab antibody positivity with patients who experience the same types of TEAEs but who remain treatment-emergent anti-ixekizumab

antibody negative. Anti-ixekizumab antibody titers will also be evaluated in anti-ixekizumab antibody positive patients who experience these events.

10.3.12. Interim Analyses

An interim database lock and unblinding will occur, and interim analyses will be performed at the time (that is , a cutoff date) the last patient completes Visit 8 (Blinded Dosing Treatment Period [Period 2]), Week 16) or ETV. This interim database lock will include all data collected by the cutoff date including the data from the Extended Treatment Period (Period 3) and follow-up data from patients that have begun the Post-Treatment Follow-up Period (Period 4). The analyses from the Week 16 lock will be treated as a primary analysis because all primary and major secondary study objectives will be assessed at this time.

Additional analyses and snapshots of study data may be performed during the Period 3 or after completion of Period 4 to fulfill the need for regulatory interactions or publication purposes.

Unblinding details are specified in the blinding/unblinding plan.

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12. Appendices

Appendix 1. Abbreviations and Definitions

Term	Definition
AE	adverse event: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
AESI	adverse event of special interest
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AS	ankylosing spondylitis: currently referred to as radiographic axial spondyloarthritis (r-axSpA)
ASAS	Assessment of Spondyloarthritis International Society
ASAS HI	Assessment of Spondyloarthritis International Society Health Index
ASDAS	Ankylosing Spondylitis Disease Activity Score. In this study, it refers to the $ASDAS_{crp}$ score which includes high sensitivity C-reactive protein (CRP).
AST	aspartate aminotransferase
axSpA	axial spondyloarthritis: a single disease entity with a subset defined by the presence of clear structural damage (r-axSpA) and a subset with no clear structural damage as defined by conventional X-rays (nr-axSpA)
BASDAI50	Bath Ankylosing Spondylitis Disease Activity Index 50
BASFI	Bath Ankylosing Spondylitis Functional Index
BASMI	Bath Ankylosing Spondylitis Metrology Index
BCG	Bacillus Calmette-Guérin
bDMARD	biological disease-modifying antirheumatic drug
Blinding	A single-blind study is one in which the investigator and/or his staff are aware of the treatment but the patient is not, or vice versa, or when the sponsor is aware of the treatment but the investigator and/his staff and the patient are not. A double-blind study is one in which neither the patient nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the subjects are aware of the treatment received.

Term	Definition
BP	blood pressure
cGMP	current Good Manufacturing Practices
CEC	Clinical Events Committee
CI	confidence interval
CLRM	Clinical Laboratory Results Modernization
cDMARD	conventional disease-modifying antirheumatic drug
Complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
CRP	C-reactive protein
C-SSRS	Columbia–Suicide Severity Rating Scale
CSR	clinical study report
DVU	disco-vertebral unit
ECG	electrocardiogram
eCRF	electronic case report form
Enroll	The act of assigning a patient to a treatment. Patients who are enrolled in the trial are those who have been assigned to a treatment.
Enter	Patients entered into a trial are those who sign the informed consent form directly or through their legally acceptable representatives.
EQ-5D-5L	European Quality of Life–5 Dimensions–5 Level
ERB	Ethical Review Board
ETV	early termination visit
FSH	follicle stimulating hormone
GCP	good clinical practice
HBV	hepatitis B virus
HLA	human leukocyte antigen
IB	Investigator's Brochure
IBD	inflammatory bowel disease

Term	Definition
ICF	informed consent form
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
ITT	intent-to-treat: The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a patient (that is, the planned treatment regimen) rather than the actual treatment given. It has the consequence that patients allocated to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance to the planned course of treatment.
IWRS	interactive web-response system
LTBI	latent TB infection
mBOCF	modified baseline observation carried forward
MMRM	mixed-effects model of repeated measures
mNY	modified New York
MRI	magnetic resonance imaging
MTX	methotrexate
nr-axSpA	nonradiographic axial spondyloarthritis: a subset of axSpA in which there is no clear structural damage as defined by conventional imaging
NRI	nonresponder imputation
NRS	numeric rating scale
NSAID	nonsteroidal anti-inflammatory drug
PCS	physical component score
PK/PD	pharmacokinetics/pharmacodynamics
PPD	purified protein derivative
PPS	per-protocol set: The set of data generated by the subset of patients who sufficiently complied with the protocol to ensure that these data would be likely to exhibit the effects of treatment, according to the underlying scientific model.
PsA	psoriatic arthritis

Term	Definition
Q2W	every 2 weeks
Q4W	every 4 weeks
QIDS-SR16	Quick Inventory of Depressive Symptomatology-self report (16 items)
r-axSpA	radiographic axial spondyloarthritis: a subset of axSpA in which there is evidence of disease features on radiographic imaging
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SF-36 MCS	Short Form 36 mental component score
SF-36 PCS	Short Form 36 physical component score
SIJ	sacroiliac joint(s)
SpA	spondyloarthritis
SPARCC	Spondyloarthritis Research Consortium of Canada
TEAE	treatment-emergent adverse event: Any untoward medical occurrence that either occurs or worsens at any time after treatment baseline and that does not necessarily have to have a causal relationship with this treatment.
TB	tuberculosis
TNFi	tumor necrosis factor inhibitor
ULN	upper limit of normal
VAS	visual analog scale
wBC	white blood cell
WPAI-SpA	Work Productivity Activity Impairment–Spondyloarthritis

Appendix 2. Clinical Laboratory Tests

Clinical Safety Laboratory Tests to be Performed by Sponsor-Designated Laboratory

Hematology[a]:	**Serum Chemistry[a]:**
Hemoglobin	Sodium
Hematocrit	Potassium
Erythrocyte count (RBC)	Bicarbonate
Mean cell volume (MCV)	Chloride
Mean cell hemoglobin concentration (MCHC)	Phosphorus
Leukocytes (WBC)	Total bilirubin
Platelets	Direct bilirubin
Absolute counts of:	Alkaline phosphatase
Neutrophils, segmented	Alanine aminotransferase (ALT/SGPT)
Neutrophils, juvenile (bands)	Aspartate aminotransferase (AST/SGOT)
Lymphocytes	Blood urea nitrogen (BUN)
Monocytes	Uric acid
Eosinophils	Creatinine
Basophils	Calcium
Urinalysis (dipstick)[a]:	Glucose
Color	Albumin
Specific gravity	Cholesterol (total)
pH	Total protein
Protein	Calculated creatinine clearance[b]
Glucose	Creatine phosphokinase (CPK)
Ketones	Triglycerides
Bilirubin	Gamma-glutamyl transferase (GGT)
Urobilinogen	**Lipid Panel[c]:**
Blood	Low density lipoprotein (LDL)
Nitrite	High density lipoprotein (HDL)
Urine creatinine	Very low density lipoprotein (VLDL)
Leukocyte esterase	

Other Tests:	
Human immunodeficiency virus antibody (HIV)[f]	Pregnancy test (serum)[d]
Hepatitis B surface antigen (HBsAg)[f]	Follicle-stimulating hormone (FSH)[e]
Anti–hepatitis B surface antibody (HBsAb)[f]	Thyroid-stimulating hormone (TSH) and free T4
Anti–hepatitis B core antibody (HBcAb)[f]	Ixekizumab serum concentration (pharmacokinetic [PK])
Anti–hepatitis C antibody[f,h]	Partial thromboplastin time (PTT)
HBV DNA[g]	Prothrombin time/international normalized ratio (PT/INR)
High sensitivity C-reactive protein (CRP)	Immunogenicity testing (anti-ixekizumab Ab)
Purified protein derivative (PPD)[i]	
Urine pregnancy test[d] (assayed by clinical study site)	
QuantiFERON®-TB Gold test [i]	
T-SPOT®[i]	
HLA-B27	

Abbreviations: Ab = antibody; DNA = deoxyribonucleic acid; HBV = hepatitis B virus; mRNA = messenger ribonucleic acid; RBC = red blood cells; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; T4 = thyroxine; WBC = white blood cells.

[a] Unscheduled blood chemistry, hematology, and urinalysis panels may be performed at the discretion of the investigator.
[b] Cockcroft-Gault calculation is used for the calculated creatinine clearance.
[c] For the fasting lipid profile, patients are not to eat or drink anything except water for 12 hours prior to test. Fasting is not required for the screening visit (Visit 1).
[d] Serum pregnancy test for all women <60 years of age who are still of childbearing potential at Visit 1 only and will be performed centrally; after Visit 1, urine pregnancy test performed locally for women of childbearing potential.
[e] Women ≥40 and <60 years of age who have had a cessation of menses for ≥12 months will have an FSH test confirming nonchildbearing potential (≥40 mIU/mL).
[f] Test required at Visit 1 to determine eligibility of patient for the study. HBV DNA testing will be done in those patients who are HBcAb+ at screening.
[g] HBV DNA testing will be done in those patients who are HBcAb+ at screening.
[h] See exclusion criteria (Section 6.2) specific to Hepatitis C antibody. A confirmatory test for HCV will be performed if the patient is positive for HCV antibody.
[i] If the QuantiFERON®-TB Gold test, or T-SPOT® is available, it may be used instead of the PPD TB test, and may be performed locally or centrally.

Selected tests may be obtained in the event of anaphylaxis or generalized urticaria.

Hypersensitivity Tests[a]	
Anti-LY antibodies (immunogenicity)	Tryptase
LY concentration (PK)	N-Methylhistamine
	Drug Specific IgE[b]
	Basophil Activation Test[b]
	Complements
	Cytokine Panel

Abbreviations: PK = pharmacokinetic
[a] Assayed by Lilly-designated laboratory
[b] Basophil Activation test will be performed if a drug specific IgE assay is unavailable.

Appendix 3. Study Governance Considerations

Appendix 3.1. Regulatory and Ethical Considerations, Including the Informed Consent Process

Appendix 3.1.1. Informed Consent

The investigator is responsible for:

- ensuring that the patient understands the nature of the study, the potential risks and benefits of participating in the study, and that their participation is voluntary.
- ensuring that informed consent is given by each patient or legal representative. This includes obtaining the appropriate signatures and dates on the ICF prior to the performance of any protocol procedures and prior to the administration of investigational product.
- answering any questions the patient may have throughout the study and sharing in a timely manner any new information that may be relevant to the patient's willingness to continue his or her participation in the study.
- ensuring that a copy of the ICF is provided to the participant or the participant's legal representative and is kept on file.
- ensuring that the medical record includes a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign th ICF.

Appendix 3.1.2. Ethical Review

The investigator must give assurance that the ERB was properly constituted and convened as required by International Conference on Harmonisation (ICH) guidelines and other applicable laws and regulations.

Documentation of ERB approval of the protocol and the ICF must be provided to Lilly before the study may begin at the investigative site(s). Lilly or its representatives must approve the ICF, including any changes made by the ERBs, before it is used at the investigative site(s). All ICFs must be compliant with the ICH guideline on GCP.

The study site's ERB(s) should be provided with the following:

- the protocol and related amendments and addenda, current IB and updates during the course of the study
- ICF
- other relevant documents (for example, curricula vitae, advertisements)

Appendix 3.1.3. Regulatory Considerations

This study will be conducted in accordance with the protocol and with the:

- consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- applicable ICH GCP Guidelines
- applicable laws and regulations

Some of the obligations of the sponsor will be assigned to a third-party.

Appendix 3.1.4. Investigator Information

Physicians with a specialty in rheumatology will participate as investigators in this clinical trial.

Appendix 3.1.5. Protocol Signatures

The sponsor's responsible medical officer will approve the protocol, confirming that, to the best of his or her knowledge, the protocol accurately describes the planned design and conduct of the study.

After reading the protocol, each principal investigator will sign the protocol signature page and send a copy of the signed page to a Lilly representative.

Appendix 3.1.6. Final Report Signature

The CSR coordinating investigator will sign the final CSR for this study, indicating agreement that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

The CSR coordinating investigator will be selected by the sponsor. If this investigator is unable to fulfill this function, another investigator will be chosen by Lilly to serve as the CSR coordinating investigator.

The sponsor's responsible medical officer and statistician will approve the final CSR for this study, confirming that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

Appendix 3.2. Data Quality Assurance

To ensure accurate, complete, and reliable data, Lilly or its representatives will do the following:

- provide instructional material to the study sites, as appropriate.
- sponsor start-up training to instruct the investigators and study coordinators. This training will give instruction on the protocol, the completion of the CRFs, and study procedures.
- make periodic visits to the study site.

- be available for consultation and stay in contact with the study site personnel by mail, telephone, and/or fax.
- review and evaluate CRF data and use standard computer edits to detect errors in data collection.
- conduct a quality review of the database.

In addition, Lilly or its representatives will periodically check a sample of the patient data recorded against source documents at the study site. The study may be audited by Lilly or its representatives, and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

The investigator will keep records of all original source data. This might include laboratory tests, medical records, and clinical notes. If requested, the investigator will provide the sponsor, applicable regulatory agencies, and applicable ERBs with direct access to original source documents.

Appendix 3.2.1. Data Capture System

An electronic data capture system will be used in this study. The site maintains a separate source for the data entered by the site into the sponsor-provided electronic data capture system. Some or all of a patient's data will be directly entered into the eCRF at the time that the information is obtained. In instances where direct data entry is not used, the site will maintain source documentation in the trial files, and the patient's data will be transcribed into the eCRF. Paper documentation provided by the patient will serve as the source document, including a study drug administration log and an event-medication diary, that will be identified and documented by each site in that site's study file.

Data managed by a central vendor, such as laboratory test data or ECG data, will be stored electronically in the central vendor's database system. Data will subsequently be transferred from the central vendor to the Clinical Laboratory Results Modernization (CLRM).

Data from complaint forms submitted to Lilly will be encoded and stored in the global product complaint management system.

Appendix 3.3. Study and Site Closure

Appendix 3.3.1. Discontinuation of Study Sites

Study site participation may be discontinued if Lilly or its designee, the investigator, or the ERB of the study site judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

Appendix 3.3.2. Discontinuation of the Study

The study will be discontinued if Lilly or its designee judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

Appendix 4. Hepatic Monitoring Tests for Treatment-Emergent Abnormality

Hepatic Monitoring Tests

Hepatic Hematology[a]	**Haptoglobin[a]**
Hemoglobin	
Hematocrit	**Hepatic Coagulation[a]**
RBC	Prothrombin Time
WBC	Prothrombin Time, INR
Neutrophils, segmented	
Lymphocytes	**Hepatic Serologies[a,b]**
Monocytes	Hepatitis A antibody, total
Eosinophils	Hepatitis A antibody, IgM
Basophils	Hepatitis B surface antigen
Platelets	Hepatitis B surface antibody
	Hepatitis B Core antibody
Hepatic Chemistry[a]	Hepatitis C antibody
Total bilirubin	Hepatitis E antibody, IgG
Direct bilirubin	Hepatitis E antibody, IgM
Alkaline phosphatase	
ALT	**Anti-nuclear antibody[a]**
AST	
GGT	**Alkaline Phosphatase Isoenzymes[a]**
CPK	
	Anti-smooth muscle antibody (or anti-actin antibody)[a]

Abbreviations: ALT = alanine aminotransferase; AST = aspirate aminotransferase; CPK = creatinine phosphokinase; GGT = gamma-glutamyl transferase; Ig = immunoglobulin; INR = international normalised ratio; RBC = red blood cells; WBC = white blood cells.

[a] Assayed by Lilly-designated or local laboratory.

[b] Reflex/confirmation dependent on regulatory requirements and/or testing availability..

Appendix 5. Spondyloarthritis Features

To be included in Study RHCH, patients must have sacroiliitis defined radiographically according to the mNY criteria based on central reading

AND

at least one of the spondyloarthritis features (from Box 4, ASAS criteria for classification of axSpA [to be applied in patients with chronic back pain ≥3 months and age at onset of back pain <45 years]) bulleted below:

- **Inflammatory back pain (IBP):** According to experts, 4 out of 5 of the following parameters present: (1) age at onset <40 years, (2) insidious onset, (3) improvement with exercise, (4) no improvement with rest, (5) pain at night (with improvement upon getting up).
- **Arthritis:** Past or present active synovitis diagnosed by a doctor.
- **Enthesitis (heel):** Past or present spontaneous pain or tenderness at examination at the site of the insertion of the Achilles tendon or plantar fascia at the calcaneus.
- **Uveitis:** Past or present uveitis anterior, confirmed by an ophthalmologist.
- **Dactylitis:** Past or present dactylitis diagnosed by a doctor.
- **Psoriasis:** Past or present psoriasis diagnosed by a doctor.
- **Crohn's/Colitis:** Past or present Crohn's disease or ulcerative colitis diagnosed by a doctor.
- **Good response to NSAIDs:** At 24 to 48 hours after a full dose of NSAID, the back pain was not present anymore or much better.
  Note: As patients enrolling into the study should have failed 2 NSAIDs or be intolerant to NSAIDs, a doctor should assess whether patients had "good" prior response to NSAIDs.
- **Family history for SpA:** Presence in first-degree or second-degree relatives of any of the following: (a) AS, (b) psoriasis, (c) uveitis, (d) reactive arthritis, (e) IBD.
  Note: A doctor should confirm with his/her patient there was a clear diagnosis (not self-diagnosis) for any of these in first- or second-degree relatives.
- **HLA-B27:** Positive testing according to standard laboratory techniques.
- **Elevated CRP:** CRP >5.00 mg/L in the presence of back pain, after exclusion of other causes for elevated CRP concentration.

References: Rudwaleit et al. 2009; Sieper et al. 2009; Sieper et al. 2017.

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